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NOVEMBER 1951

VOLUME 63 NUMBER 5

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter July 10, 1925, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $14.00

PUBLISHED OCTOBER 1951

Atlas of
GENITO-URINARY SURGERY

by

PHILIP R. ROEN, M.D., F.A.C.S.

Instructor in Urology, New York Postgraduate Medical School; Clinical Instructor in Urology, New York Medical College; Associate Visiting Urologist, Morrisania City Hospital; Assistant Attending Urologist at Midtown Hospital and Yonkers General Hospital; Civilian Consultant in Urology, U. S. Air Force, Mitchel Field Air Base Station Hospital; Diplomate, American Board of Urology.

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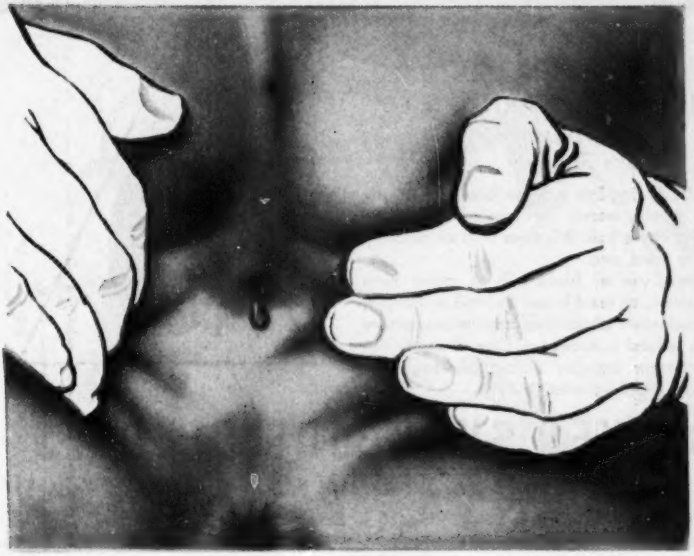

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Wright, L. T., et al.: Antibiotics & Chemotherapy 1:165 (June) 1951

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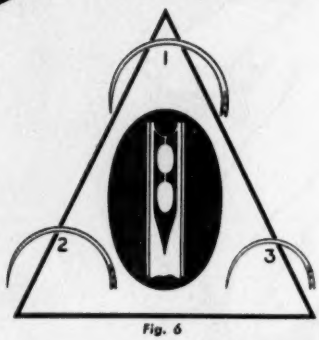

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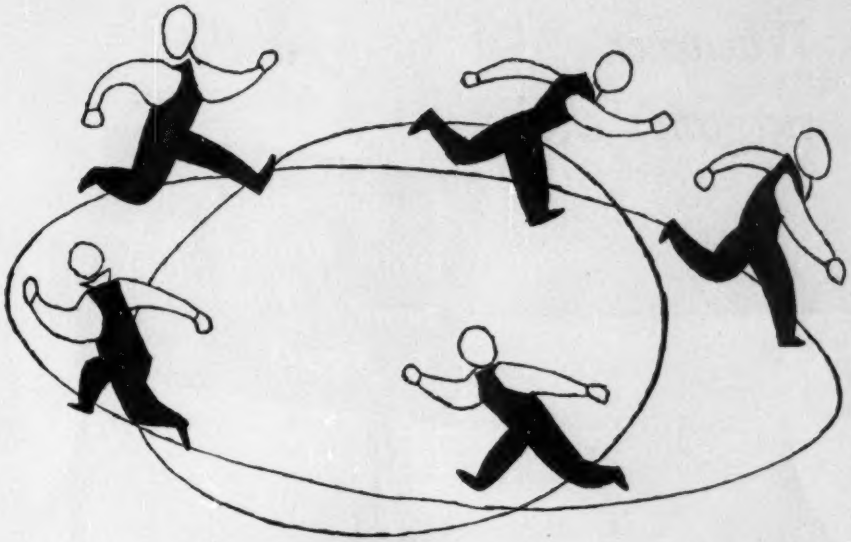

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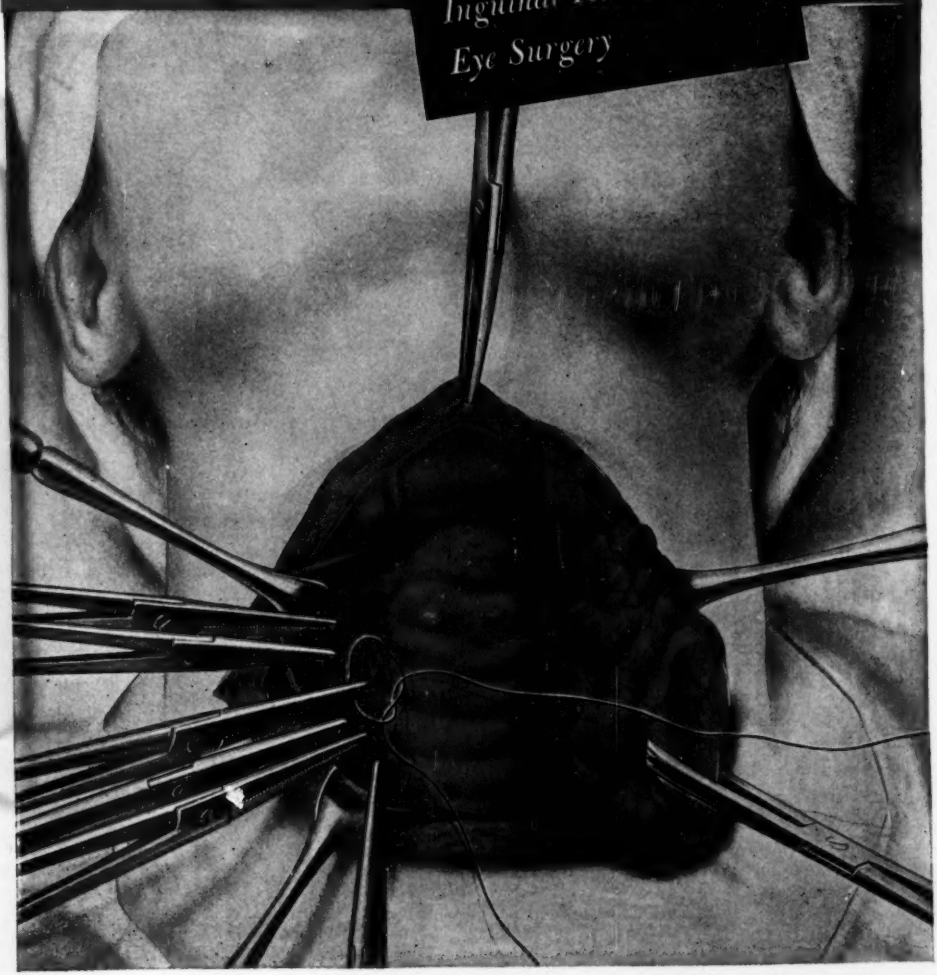

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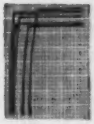

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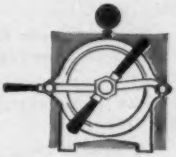

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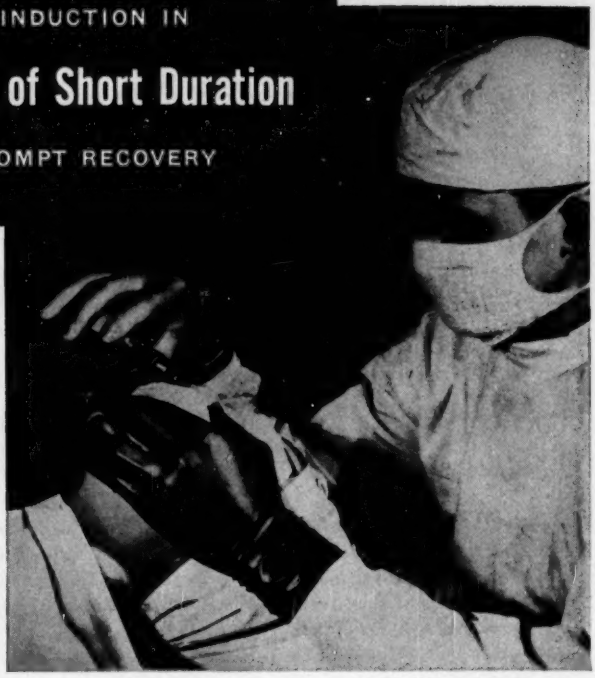

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VOLUME 63 NOVEMBER 1951 NUMBER 5

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Editorial

HYALURONIDASE IN EXCRETORY UROGRAPHY

The spreading factor of Duran-Reyals, hyaluronidase, has been advocated for two clinical purposes: one, as an addition to semen perhaps to facilitate dispersion of the cumulus oophorus and increase the chances of fertilization, and, the other, as an adjunct to subcutaneous therapy to allow rapid dispersion and absorption of parenterally administered fluids.

Surgeons, and more especially urologists, appear to have failed to make use of this substance in excretory urography. Hechter, Dopkeen and Yudell reported in the *Journal of Pediatrics* in 1947 that hyaluronidase greatly increased the rate of absorption of hypodermoclyses and detected no toxic reactions. Toxicity is apparently absent, and the incidence of sensitivity to the commercial extract derived from the testes of bulls is as low as 0.4%. One instance of contact dermatitis has been reported.

Mention of the use of hyaluronidase to hasten the uptake of dye in excretory urography in infants has appeared in several papers dealing with the general applicability of the substance. Urologists have long recognized the inferiority of subcutaneous urograms compared with those made by intravenous administration. The slow absorption results in delayed excretion, with absence of any high concentration in the renal pelvis. Hyaluronidase offers a safe means of obtaining films comparable to the intravenous ones.

We use 150 turbidity units of hyaluronidase dissolved in 5 cc. of sterile water. This is injected through two needles placed subcutaneously over the scapulae, after which 10 cc. of 35% diodrast® diluted to 50 cc. with sterile saline is slowly injected on each side. (An alternative method, which we have not yet given a trial, is the simultaneous injection of hyaluronidase with the diodrast.®) The child, previously placed prone to retard air swallowing, is turned supine and films made at 5 and 15 minutes and at later intervals if necessary. While statistical proof is still lacking, the clinical results to date have been gratifying.

An additional use of hyaluronidase is in conjunction with the phenolsulfonphthalein renal function test, since the curve which results from the use of hyaluronidase more closely follows that after intravenous injection.

FRANK HINMAN, JR., M.D.

EXPERIMENTAL SURGICAL TECHNIQUES IN MITRAL STENOSIS

EMANUEL MARCUS, M.D., Ph.D.
With the Technical Assistance of Samuel N. T. Wong, M.D.
CHICAGO

SURGEONS have been interested in mitral stenosis, experimentally, for more than half a century.[1] Logically, this interest first became manifest as an attempt to produce stenosis of the mitral valve in the experimental animal. If the disease could be reproduced in animals, the relative merits of various surgical technics for the relief of the sequelae of mitral stenosis could more easily be determined. On the basis of information so gained, proper application to this disease in human beings might be made without resort to trial and error in clinical cases. Such application could be perfectly valid, even though the disease as it occurs naturally in human beings, a cicatricial stenosis consequent upon healing of an infectious granuloma, and that obtained in the animal have a different mechanism of production.

The primary aim of corrective surgical treatment is the relief of the dynamic disturbances of circulation caused by the valvular narrowing, viz., the engorged pulmonary circulation on one side of the valve and the decreased left ventricular output on the other. The impediment to the flow of blood from the left auricle to the left ventricle during cardiac diastole results progressively in a large, distended left auricle, vascular congestion of the lungs, and, ultimately, dilatation and hypertrophy of the right ventricle. The characteristic pulmonary findings necessary for correction if acute cardiorespiratory episodes are to be avoided are classically described by Parker and Weiss.[2]

Dr. Marcus is instructor in surgery, The Chicago Medical School.

From the Laboratory of Cardiology and the Department of Surgery, The Chicago Medical School.

1. (*a*) Samways, D. W.: Cardiac Peristalsis: Its Motions and Effects, Lancet **1**:927, 1898. Brunton, L.: (*b*) Preliminary Note on Possibility of Treating Mitral Stenosis by Surgical Methods, ibid. **1**:352, 1902; (*c*) Surgical Operation for Mitral Stenosis, ibid. **1**:547, 1902. (*d*) Cushing, H., and Branch, J. R. B.: Experimental and Clinical Notes on Chronic Valvular Disease in Dog, and Possible Relations to Future Surgery of Cardiac Valves, J. Med. Res. **17**:471, 1907. (*e*) Bernheim, B. M.: Experimental Surgery of Mitral Valve, Bull. Johns Hopkins Hosp. **20**:107, 1909. (*f*) Schepelmann, E.: Herzklappenchirurgie: Experimentelle Untersuchungen, Deutsche Ztschr. Chir. **120**:562, 1912-1913. (*g*) Jeger, E.: Die Chirurgie der Blutgefässe und des Herzens, Berlin, Hirschwald, 1913. (*h*) Cutler, E. C., and Levine, S. A.: Cardiotomy and Valvulotomy for Mitral Stenosis, Boston M. & S. J. **188**:1023, 1923. (*i*) Cutler, E. C.; Levine, S. A., and Beck, C. S.: Surgical Treatment of Mitral Stenosis: Experimental and Clinical Studies, Arch. Surg. **9**:687 (Nov.) 1924. (*j*) Cutler, E. C., and Beck, C. S.: The Present Status of Surgical Procedures in Chronic Valvular Disease of the Heart: Final Report of All Operative Cases, ibid. **18**(Pt. 2):403 (Jan.) 1929. (*k*) Allen, D. S., and Graham, E. A.: Intracardiac Surgery—New Method: A Preliminary Report, J. A. M. A. **79**:1028 (Sept. 23) 1922.

2. Parker, F., Jr., and Weiss, S.: Nature and Significance of Structural Changes in Lungs in Mitral Stenosis, Am. J. Path. **12**:573, 1936.

PRODUCTION OF STENOSIS

The first recorded attempts to produce a stenotic lesion of the mitral valve were by Samways [1a] in 1898 and by Brunton [1b,c] in 1902. The first attempts in this country were by Cushing and Branch [1d] in 1907 and by Bernheim [1e] in 1909. In 1943 Shaw, Adams, Rasmussen, Hrdina, and Aronson [3] produced stenosis in animals who lived usually a few minutes to a few hours, with only one dog surviving 25 days. The technical difficulties of producing a stenosis of the valve while blood is coursing through the chambers of the heart are great and constitute the reason for short survivals. By transventricular suture we have produced stenosis of the mitral valve in dogs who then lived two to five days and died of excessive interference with the coronary blood supply to the left ventricle. When the same operation was accomplished through the auricular wall, the animals lived 4 to 16 weeks. In two cases it was noted at autopsy that the cotton sutures had cut through and stenosis no longer existed. Supporting evidence of existing stenosis (before subsequent surgical procedures or autopsy) included phonocardiograms and exercise tolerance. Connolly [4] has recently reported a similar technic.

With the development of technics for the exclusion of blood from the chambers of the heart,[5] it is to be expected that intracardiac procedures of various nature will be possible with indefinite survival. For this reason we, too, have now turned to this distinctly advantageous adjunct to intracardiac surgery.

ATTEMPTS AT REMEDIAL SURGICAL PROCEDURES

Historical Aspects.—Varied have been the avenues of surgical approach to the solution of the problem of pulmonary hypertension in mitral stenosis, both direct and indirect. Jarotsky [6] first made the suggestion that an interauricular defect be created to simulate the Lutembacher [7] syndrome. Patients with such a combination of lesions still have pulmonary hypertension. However, the hypertension is mostly due to the increased stroke volume of the right ventricle, while the pressure in the

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pulmonary veins and in the left auricle is lower. It remained for others [8] in this country, years later, to try this thesis experimentally. These excellent investigators found this solution wanting.

Bland and Sweet [9] attempted to relieve the pulmonary load, although partially and indirectly, by anastomosing the pulmonary vein of the dorsal segment of the lower lobe of the right lung to the azygos vein. Again, although some temporary relief was thereby afforded, others [10] have pointed out the unphysiologic nature of such a partial short circuit. It should also be emphasized that while the Bland-Sweet procedure relieves pulmonary hypertension partially and temporarily it does not increase left ventricular output.

Allen and Graham,[1k] Cutler and Levine,[1h,l] and Cutler and Beck [1j] essayed corrective procedures more than 25 years ago. Harken, Ellis, Ware, and Norman,[8d] Bailey, Glover, and O'Neill,[11] Baker, Brock, and Campbell,[12] and Murray, Wilkinson, and MacKenzie [13] have made direct approaches to the problem by intervening at the very site of the stenosed valve ring, which they cut in several ways. Most of the technics of cutting the stenosed valves led to sudden gross mitral regurgitation and rapid death. The Canadian group [13] attempted to reconstruct, across the left ventricle, a valve of tendon and vein composition to compensate for the equally serious, or even more serious, regurgitation which replaced the stenosis. The procedure was uncertain and unphysiologic and involved a complex surgical exercise. The New England group [8d] preferred wedge resection of the valve; the British group [12] preferred to punch out sections of the cicatrix, the sections being 180 degrees from each other; the American group [11] preferred to incise the cicatrix where the commissure existed normally—hence the term commissurotomy rather than valvulotomy.

Another attempt at construction of a mitral valve to avoid the gross regurgitation produced when the valve is destroyed for stenotic disease was recently reported by Denton, Mastriani, Brown, and Wiggers.[14] This valve was constructed entirely

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of polythene and depended for prevention of reflux from ventricle to auricle on the chance approximation of a hard foreign body to endocardial surface—grossly unphysiologic.

Jeger,[15] in Germany in 1913 suggested, but did not carry out, a shunt from the pulmonary vein to the left ventricle. In 1948 Rappaport, Murray, and Davies [15] and in 1950 Rappaport and Scott [16] discussed the implantation of the left auricular appendage into the left ventricle to bypass the mitral valve. Bill, Pierce, and Gross [17] reported on a procedure almost identical to ours for anastomosing the left atrial appendage to the left ventricle with the use of various intervening graft mediums.

EXPERIMENTAL PROCEDURE

To test the surgical feasibility of bypassing the mitral valve by chamber anastomosis (versus the commissurotomy operation), we have attempted this procedure 20 times in the following six different ways:

1. Implantation of the left auricular appendage into the left ventricle so that the appendage opening lay between the wall of the ventricle and the chordae tendineae attending the anteromedial valve: Four dogs.

2. Implantation of the auricular appendage into the left ventricle proximal to the anterior coronary vessels, through the auriculoventricular ring, attempting to place the appendage between the ventricle wall and the anteromedial valve: Two dogs.

3. Anastomosis of the auricular appendage to a segment of arterial graft, which was then implanted into the left ventricle through its wall: Two dogs.

4. Same as Technic 3, using a vein graft: Two dogs.

5. Same as Technics 3 and 4, using a vein-lined vitallium® tube: Two dogs.

6. Same as Technics 3, 4, and 5, using a heparinized, fashioned curved polythene tubing (nonwetting), with flanges at both ends to secure fixation within the ventricular wall: Eight dogs.

The animals were anesthetized with veterinary 3% pentobarbital (nembutal®) solution, given intraperitoneally in a dose of 35 mg. per kilogram of body weight, and atropinized with 0.4 to 0.8 mg. of atropine sulfate. Entry to the chest was gained by an intercostal approach, usually through the left fourth intercostal space. Respiration was controlled by an artificial-respiration apparatus through an intratracheal tube equipped with an inflatable cuff.

RESULTS

All the listed procedures are not difficult of accomplishment, but all leave much to be desired, even though the underlying principle is logical.

In the case in which the auricular appendage was implanted directly into the ventricle, whether by Technic 1 or 2, it was found that the resistance of the ventricle wall was an impediment to the flow of blood from the appendage to the left ventricular chamber. This was true even in ventricular diastole. Indeed, in the cases in which the implant was placed through the auriculoventricular ring proximal to the coronary vessels, the close application of the base of the mitral valve to the anteromedial wall of the ventricle did not permit of adequate space for the implanted appendage to transmit an unimpeded flow of blood. When the appendage was implanted distal to the coronary vessels, between the ventricular wall and the

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chordae tendineae attending the anteromedial valve, it was difficult to avoid damage of the chordae with certainty. Anastomosis of the appendage to the ventricle via an intervening arterial or venous graft was tried in an endeavor to perform less surgery in the ventricular wall. Also, it was thought that the vessel might constitute an automatic valve, not permitting reflux from the ventricle with its higher pressure to the atrium. Thrombosis of these grafts proved even more troublesome than thrombosis of the direct atrial implants. Except for ease of handling, the vein-lined vitallium®-tube graft offered no advantage.

It remained for the experiments with fashioned curved polythene tubing to give the best results. Polythene tubing which is nonwettable was used; it was heparinized in advance of use. These tube grafts were fashioned by heat from long lengths of tubing as supplied by the manufacturer; flanges were fashioned at the ends for firm anchorage into both the ventricle wall and to receive the purse-string suture that anchored it into the atrial appendage. The tube was so curved that the appendage would not be disturbed from its normal position, and yet its distal end traversed the wall of the left ventricle perpendicular to the surface of that wall. The rigidity of the polythene resists compression by the muscular contraction of the heart wall. These tube grafts transmitted blood as long as the animal's blood was heavily heparinized, in a retrograde fashion when placed in a normal dog's heart, and from atrium to ventricle when the mitral valve was effectively obstructed. It is this group of experiments which most closely resembles the procedure of Bill, Pierce, and Gross [17] to which we previously referred. In any event, when heparinization was discontinued, thrombosis occurred in the shunt.

COMMENT

Many advances in the surgical therapy of well-recognized diseases are consequent upon a fuller understanding of the basic physiologic principles established in the laboratory. During the past 25 years many new operations have been suggested and tried for treatment of diseases previously not falling within the realm of known surgical repertoire. In retrospect, it becomes apparent that only the most physiologic, the least unnatural, procedures have withstood clinical trial as judged by results. This evolutionary progress is being repeated in all the subdivisions of thoracic surgery, especially those of cardiac and vascular problems. Even though many procedures are superseded by others, they contribute to the ever-widening interest in operative treatment of clinical conditions heretofore considered irreversible.

Our endeavor to sift the numerous procedures proposed for the remedy of sequelae of mitral stenosis has again affirmed the basic truths above enunciated. All the technics reported in the literature and those herein tried experimentally are technically feasible. However, because of objections to most of these procedures, there is one operation, in our opinion, which appears to be the most physiologic and the least unnatural. Attempts at reproduction of a Lutembacher syndrome by making an atrial septal defect have been found short of desirability mainly because of added direct strain to the right side of the heart without increase in the output of the left side of the heart.[8] The anastomosis of a pulmonary vein to the azygos vein [9] merely diverts a fraction of the return to the left auricle and redirects it to the right auricle, with only partial relief of pulmonary hypertension plus the imposition of an increased load on the right side of the heart.[10] Anastomosis of the

two chambers, left auricle and left ventricle, by implantation of the atrial appendage through the left ventricular wall [18] has been found to be technically too complex a procedure and to require dangerous continuous heparinization. Anastomosis of the two chambers via an intervening graft of vein, artery, vein-lined vitallium® or polythene tubing, as herein reported and almost identical to the technic reported by Bill, Pierce, and Gross,[17] although more lasting than the other procedures, is also wanting. The polythene, as is true of any solid foreign body, is bound to erode soft tissue, particularly moving tissue such as the heart and all the structures of the mediastinum. This was found to be the case.

It falls, then, to the simple, direct attack of cutting the stenosed valve by a technic that will produce the greatest remedial effect and the least disturbance (in this instance, mitral regurgitation) to withstand the test of time. Of the various methods of cutting the cicatrix,[19] at once the simplest and most effective appears to be that of Bailey, Glover, and O'Neill.[11] They endeavor to cut what was the commissure between the leaflets—hence the term commissurotomy. This procedure produces the least amount of regurgitation and requires no further complex surgical maneuvers or foreign bodies to correct the evils of an appreciable regurgitation.

SUMMARY AND CONCLUSIONS

The evolution of surgical therapy of mitral stenosis is reviewed.

The inability to produce mitral stenosis by either transventricular or transauricular approach with survival beyond a few weeks is confirmed. This is true if the operation is accomplished while the heart is functioning. It is hoped that with exclusion of blood from the chambers with new apparatus indefinite survivals will be possible.

Various methods of anastomosing the chambers of the left side of the heart to each other are presented experimentally and reviewed from the literature.

All such indirect methods are found to have undesirable features; to wit, thrombosis of grafts, interference with normal structures, erosion of soft tissue by foreign bodies. They are, therefore, considered unnatural and are not to be recommended for clinical application.

The most physiologic and least disturbing operation for relief of the sequelae of mitral stenosis is the commissurotomy of Bailey, Glover, and O'Neill.[11]

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SOME STUDIES ON CLOTTING ACTIVITY OF EXTRACTS OF NORMAL AND DISEASED TISSUES

A. BLAUSTEIN, M.D.
C. HUBER, M.D.
AND
M. ALBERIAN, B.S.
NEW YORK

COMPONENTS of the coagulation mechanism have been and are being extensively investigated in relation to the development of thrombosis. Most recently, Ochsner and his associates [1] have demonstrated the lowering of circulating antithrombin postoperatively, and they feel that this may play a role in the development of postoperative thrombosis. McFarlane [2] feels that trauma may cause extensive damage to tissues and blood vessels, with inevitable absorption of thromboplastin and thrombin. Ochsner [1] states that a predisposing factor to phlebothrombosis is the increased coagulability of the blood which occurs in persons subjected to tissue trauma. He further states that, whatever the cause, tissue damage results in blood changes which increase the coagulability of blood. Allen, Barker, and Hines [3] observed that postoperative thrombophlebitis is commonest after procedures in which considerable tissue is removed and in which there is likely to be a great amount of tissue injury. Mason and Harrison [4] described experiments demonstrating the ability to develop thrombosis and pulmonary embolism in dogs and in vitro in an experimental system with the use of tissue extracts. Waugh and Ruddick [5] found no evidence that the prothrombin concentration of the blood ever rises above the normal optimum level. It has never been demonstrated that variations in the level of calcium in the blood under normal or even pathological conditions are sufficient to affect appreciably the speed of the coagulation process. They concluded that an increase in the only remaining factor, namely, thromboplastin, is the cause of an accelerated coagulability. Astrup and Darling [6] in 1942 and Astrup [7] in 1944

This study was supported by a grant from the Abbott Laboratories, North Chicago, Ill.

Dr. Blaustein is Chief of the Division of Hematology, Gouverneur Hospital, New York, and the Laboratory of the Bayonne Hospital, Bayonne, N. J.

Dr. Huber is Resident in Surgery, New York Polyclinic Medical School and Hospital, New York.

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studied the thromboplastic activity of normal human tissues. It was felt that it would be interesting to make tissue extracts of fresh surgical and postmortem specimens received in the pathology laboratory and to study their clotting activity.

MATERIALS AND METHODS

Materials.—Two hundred fifty-nine surgical and postmortem specimens received in the laboratory were utilized. They were roughly grouped according to systems as shown in the section under Comment.

Methods.—Preparation of Tissue Extracts: The extracts were made within one hour of surgical or postmortem removal of the specimen. Blocks of tissue were cut, and 1 gm. was carefully weighed. We attempted to rid the tissue of blood vessels and blood as well as could be done. The specimen was ground up in a mortar and suspended in 2 cc. of saline solution. The suspension was treated according to the method described by Ware and Seegers[8] for preparation of their crude lung extracts. The extracts were placed in the refrigerator at 4 C. for 48 hours. At the end of this time they were centrifuged at 5,000 rpm, and the supernatant fluid was used as the thromboplastic agent. In order to test for thrombin activity, 1% fibrinogen solution was used in the manner of assaying for thrombin. Fibrinogen activity was checked for in a similar manner, using a thrombin solution containing 100 units per milliliter. In both cases no clot was obtained, eliminating the possibility of active thrombin or measurable fibrinogen playing a role. Samples in which feces were present were carefully washed 10 times with saline solution prior to preparation of the extracts. Some of the stomach preparations proved to be too mucoid; the prothrombin readings were difficult to estimate, and some of the results had to be discarded.

In a number of instances several blocks were cut from a single specimen. Extracts were made from these blocks in order to observe possible variations in clotting activity from different portions of the same specimen. The differences were found to be negligible.

A sample of normal plasma was assayed each day the extracts were tested. The prothrombin time was determined by the Quick one-stage method, and a standard commercial thromboplastin, maltine,* was used. The tissue extract was then substituted as the thromboplastic agent and the prothrombin time redetermined. The normal control prothrombin readings ranged from 13 to 15 seconds.

Methods of Evaluating Data: 1. Any tissue extract clotting normal plasma in less than 20 seconds was considered to show marked thromboplastic activity.

2. The clotting activities of normal and of diseased tissue were compared whenever possible.

3. The clotting activities of tissues involved by different pathological processes were compared with one another.

COMMENT

Thyroid Gland.—Twenty-one tissue extracts were made. Eleven of these were of colloid adenomas; eight were of toxic hyperthyroid goiters, and two were of papillary adenocarcinomas. Of the 11 extracts of colloid adenomas, 3 clotted normal plasma in less than 20 seconds. The extracts of all eight toxic thyroid glands clotted the plasma in less than 20 seconds. The carcinomatous extracts fell within the range noted for the colloid adenomas.

Adrenal Gland.—A single large adrenocortical carcinoma was studied. The tissue extract clotted the control plasma in 14 seconds and in up to a 1 : 10 dilution still showed clotting activity in less than 20 seconds.

Tonsils.—Ten tonsils removed from children in the age group of 2 to 6 years were studied. None of these tonsils was infected, but some were hypertrophied. None of the tissue extracts clotted plasma in less than 20 seconds.

8. Ware, A., and Seegers, W.: Am. J. Clin. Path. **19**:471, 1949.

Stomach.—Fifteen extracts of stomach tissue were made. Eight of these were from histologically normal tissue; three were from gastric ulcers, and four were from neoplasms. Five of the eight normal tissue extracts clotted the control plasma in 20 seconds or less; tissue extracts from three of the four neoplasms clotted the normal plasma in less than 20 seconds. The tumor whose extract did not clot the plasma in 20 seconds was a scirrhous carcinoma. All three extracts from ulcers clotted the plasma in less than 20 seconds. No differences were observed in comparing one part of the stomach with another. Of the 15 tissue extracts, 11 clotted the plasma in less than 20 seconds.

Colon.—Four extracts of normal sigmoid, 11 of malignant neoplasms, and 1 of benign adenoma were studied. All but one extract clotted normal plasma in less than 20 seconds, and this extract, clotting normal plasma in 46.6 seconds, was from a scirrhous carcinoma. There did not appear to be any difference in clotting activity between normal and neoplastic tissue of the colon.

Appendix.—Twenty-four appendical extracts were studied. Twelve of these appendixes were histologically normal, and 12 showed acute suppurative inflammation. Of the 12 inflamed appendixes, extracts of 8 showed clotting activity in less than 20 seconds. Of the 12 normal appendixes, extracts of 4 showed clotting activity in less than 20 seconds.

Gall Bladder.—Twenty extracts were examined, 5 of which were from histologically normal organs; 11 were from organs which had the histological appearance of chronic cholecystitis, and 4 were samples of fresh bile. The normal extracts varied in their clotting activity of control plasma from 13 seconds to no activity at all. Extracts of the chronically inflamed gall bladders varied in clotting activity from 17.8 seconds to none at all. None of the samples of bile clotted normal plasma. It was interesting to observe that extracts of gall bladders heavily inspissated with bile showed no clotting activity. Only 2 of the 20 extracts clotted the plasma in less than 20 seconds. One was an extract from histologically normal tissue and the other from a chronically inflamed gall bladder.

Uterus.—Endometrium: Twelve extracts were studied. Five of these were of endometrium in the proliferative phase and five in the secretory phase. One was of a polyp, and one was of an adenocarcinoma. All of the samples of proliferative endometrium clotted normal plasma in less than 20 seconds, while none of the samples of the secretory endometrium did. The clotting activity of the extracts of polypoid endometrium and adenocarcinoma fell within the range of activity for proliferative endometrium.

Corpus Uteri.—Thirty-one tissue extracts of myometrium were studied. Three of these were of histologically normal myometrium from the uteri of women in the 30- to 40-year age group. Twenty-six were extracts of fibromyomas, and two were extracts of parturient uteri. Only one of the latter extracts clotted the control plasma in less than 20 seconds. The extracts of fibromyomas varied in their clotting activity from 27.5 to 115 seconds.

Cervix.—Nine tissue extracts were studied. Five of these were of histologically normal tissue; two were of endocervical polyps, and two were of tissue showing extensive epidermoid carcinoma. The histologically normal tissue varied in its

clotting activity from 20.2 to 47.3 seconds. Both extracts of polyps clotted the plasma in less than 20 seconds. The clotting activity of the extracts of epidermoid carcinoma fell within the range of that found for histologically normal tissue.

Fallopian Tube.—Twenty extracts were assayed, including 13 of histologically normal tissues; 3 were of tissue from cases diagnosed as hydrosalpinx; 2 were from cases of chronic salpingitis, and 2 were from cases of ectopic pregnancy. Extracts of 8 of the 13 histologically normal tissues clotted the control plasma in less than 20

TABLE 1.—*Clotting Activity of Organ Extracts from a Twin Six-Month Pregnancy*

Organ Extract	Control Prothrombin Time, Sec.	Clotting Time of Tissue Extract of Twins, Sec.	
		A	B
Thymus	15	24.6	27.1
Lung	15	14.2	14.0
Heart	15	15.5	21.6
Spleen	15	27.4	27.8
Liver	15	30.9	34.1
Pancreas	15	21.2	20.4
Small bowel	15	16.2	15.0
Large bowel	15	17.3	18.5
Kidney	15	18.9	20.5

TABLE 2.—*Thromboplastic Activity of Tissue Extracts*

Tissue	No. Extracts Studied	No. Clotting Normal Plasma in Less Than 20 Sec.
Thyroid	21	11
Prostate	12	9
Stomach	15	11
Colon	16	15
Appendix	24	12
Fallopian tube	20	10
Uterus	43	6
Cervix	9	2
Ovary	17	..
Breast	22	4
Tonsils	10	..
Gall bladder	20	2
Varicose veins	10	1
Total	229	83

seconds. The remaining tissue extracts clotted the control plasma in the same range of time as the histologically normal tissue extracts. A total of 10 extracts clotted the normal plasma in less than 20 seconds.

Ovary.—Seventeen extracts were studied. Four were of follicular cysts, two of follicular cyst fluid, three of corpus luteum cysts, two of serous cystadenomas, two of fluid from the serous cystadenomas, and two of Krukenberg tumors; one extract was of an adenocarcinoma, and one of a granulosa-cell tumor. None of these extracts clotted normal plasma in less than 20 seconds.

Breast.—Extracts of 22 tissue samples were studied. Of these, 3 were samples taken from plastic operations, and no histological changes were noted. Eight extracts were of fibroadenomas and 11 were of adenocarcinomas. Of the 22 extracts,

TABLE 3.—*Comparison of Clotting Activity of Extracts of Normal and Diseased Tissue*

Lesion	No. of Extracts	Control Prothrombin Time, Sec.	Clotting Activity of Tissue Extracts,* Sec.
Breast			
Histologically normal tissue	3	13-14	36.6-43.9
Fibroadenomas	8	13-14	18.5-45.5
Adenocarcinomas	5	13-14	16.8-26.7
Medullary carcinoma	1	13-14	40.1
Scirrhous carcinoma	5	13-14	18.4-41.0
Thyroid Gland			
Colloid adenomas	11	13-14	15.0-62.0
Toxic hyperthyroid goiter	8	13-14	8.1-15
Papillary adenocarcinomas	2	13-14	17.2-26.9
Adrenal Gland			
Adrenocortical carcinoma	1	13-14	1:10 dilution, 16 1:20 dilution, 20 1:30 dilution, 25 1:50 dilution, 50
Tonsils			
Normal	10	13-14	21.6-78.0
Stomach			
Histologically normal tissue	8	13-15	15.3-20.3
Gastric ulcers	3	13-15	13.5-20.7
Ulcerating adenocarcinoma	3	13-15	16.7-19.3
Scirrhous carcinoma	1	13-15	46.5
Appendix			
Histologically normal tissue	12	13-15	16.5-25.7
Acute suppurative inflammation	12	13-15	12.2-20.4
Colon and Rectum			
Histologically normal sigmoid	4	13-15	11.1-17.3
Adenocarcinoma of sigmoid and rectum	10	13-15	17.0-20.3
Scirrhous carcinoma of sigmoid	1	13-15	46.6
Benign adenoma of sigmoid	1	13-15	16.4
Gall Bladder			
Histologically normal tissue	5	13-15	13.0-infinity
Chronic cholecystitis	11	13-15	17.8-infinity
Fresh bile	4	13-15	No clot
Endometrium			
Proliferative endometrium	5	13-15	15.3-17.9
Secretory endometrium	5	13-15	22.7-42.7
Polyp	1	13-15	22.5
Adenocarcinoma	1	13-15	32.8
Corpus Uteri			
Histologically normal tissue	3	13-15	24.7-28.6
Fibromyomas	26	13-15	27.5-115.0
Parturient uteri	2	13-15	18.7-45.5
Cervix			
Histologically normal tissue	3	13-15	20.2-47.3
Endocervical polyp	2	13-15	19.6-20.0
Hypertrophy	2	13-15	21.0-29.0
Epidermoid carcinoma	2	13-15	23.9-34.0
Fallopian Tube			
Histologically normal tissue	13	13-15	11.8-33.6
Hydrosalpinx	3	13-15	15.6-30.9
Chronic salpingitis	2	13-15	18.3-23.6
Ectopic pregnancy	2	13-15	17.9-25.8
Ovary			
Follicular cysts	4	13-15	30.4-82.0
Follicular cyst fluid	2	13-15	No clot
Corpus luteum cyst	3	13-15	26.2-57.6
Serous cystadenomas	2	13-15	44.3-53.3
Serous cystadenoma fluid	2	13-15	No clot
Granulosa-cell tumor	1	13-15	42.1
Krukenberg tumor	2	13-15	27.2-30.3
Adenocarcinoma	1	13-15	37.8
Prostate Gland			
Benign prostatic hypertrophy	10	13-15	13.4-21.6
Adenocarcinoma	2	13-15	15.4-26.3
Varicose Veins			
Varicosities	10	13-15	18.5-34.0

* Measured by prothrombin time determination on normal plasma, using a commercial thromboplastin and repeated with substitution of the tissue extract as the thromboplastic agent.

only 4 clotted the control plasma in less than 20 seconds. One of these was an extract from a fibroadenoma, and the other three extracts were of adenocarcinomas.

Prostate Gland.—Twelve extracts were studied. Ten of these were of tissue showing benign hypertrophy and two were of adenocarcinomas. Nine of the 12 clotted the control plasma in less than 20 seconds. The clotting activity of the adenocarcinoma extracts fell within the range found for extracts of benign hypertrophic glands.

Varicose Veins.—Ten samples were studied. An extract of only one of this group clotted the control plasma in less than 20 seconds.

Fetal Organs.—A comparison was made of the clotting activity of extracts of organs removed at autopsy from a twin six-month pregnancy in which no underlying pathological change was found.

Analysis of Data.—Thyroid gland extracts showed marked thromboplastic activity. The extracts of the toxic hyperthyroid goiters seem more active than those of colloid adenomas. The prostate gland has always been known to be rich in thromboplastin, and hypertrophy of the gland does not appear to diminish this activity. The stomach and colon are rich in thromboplastin. No change due to inflammatory or neoplastic lesions can be detected. Acute inflammation distinctly enhances the thromboplastic activity of the appendix. The normal Fallopian tube is rich in thromboplastin, and this is not appreciably altered by inflammatory lesions. The uterus, cervix, ovary, breast, tonsils, gall bladder, and varicose veins are not as rich in thromboplastin as the organs described above. The parturient uterus showed marked thromboplastic activity, but this was probably due to the placental and decidual tissue present. Lesions of the ovary showed little thromboplastin activity.

The observations made on the tissues removed from the set of twins demonstrate the interesting fact that their tissues possess similar thromboplastic activity.

The majority of tumors were rich in thromboplastin; however, these growths arose in tissues that are in themselves rich in thromboplastin.

Two patients whose surgical specimens were studied had pulmonary embolism. One patient had had a breast resection for adenocarcinoma. The tissue extract clotted normal plasma in 16.8 seconds. The pulmonary embolism did not prove fatal. The other patient had had a carcinoma of the sigmoid, and the tissue extract clotted normal plasma in 17 seconds. The patient died, and postmortem examination revealed pulmonary embolism.

CONCLUSIONS

One cannot state that the fact that a tissue extract clots normal plasma in less than 20 seconds may be of significance in the pathogenesis of thrombosis, but it can be said with certainty that such extracts possess marked thromboplastic activity. It must be further emphasized that the study of isolated portions of tissue gives no clue concerning the amount of tissue juice that may be released and absorbed in any given surgical procedure. Other questions that remain to be answered are the effects of dilution of tissue extracts finding their way into the blood stream, the action of antithromboplastin, and whether the absorption of the thromboplastin leads to a temporary hypercoagulability that may facilitate the formation of a thrombus in a limb where the venous return is slowed.

SUMMARY

Tissue extracts were made from 259 surgical and postmortem specimens. Their clotting activity was studied by employing them as thromboplastic agents, after assaying a normal plasma with the use of a commercial thromboplastin.

Extracts that clotted the control plasma in less than 20 seconds were considered to possess marked thromboplastic activity.

Certain tissues and their lesions were noted to be rich in thromboplastin, while others were poor in this material.

The appendix is rich in thromboplastin, and acute inflammation enhanced the thromboplastic activity of that organ.

The tumor extracts studied were rich in thromboplastin. Scirrhous tumors were poor in this substance.

Comparisons were made of the clotting activity of extracts from the tissues of twin fetuses. Their clotting activities were found to be almost identical.

Proliferative endometrium is rich in thromboplastin, while secretory endometrium is poor in this material.

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INCREASED INTRACRANIAL PRESSURE FOLLOWING RADICAL NECK SURGERY

R. K. JONES, M.D.
CHICAGO

THE PURPOSE of this paper is to illustrate the marked increase in intracranial pressure that occurs after radical operations on the neck and the methods used in an attempt to overcome this abnormality.

The most acceptable therapy for cancer of the head and neck is wide surgical excision. Radical neck dissection involves removal of the superficial and deep cervical structures, including the sternocleidomastoid muscle, the external and internal jugular veins and the entire block of tissue containing the superficial and deep cervical lymphatic vessels. This procedure, therefore, requires the removal of the internal jugular vein from the base of the skull to the base of the neck. That such is the accepted practice is indicated by several papers and communications.[1]

The cases herein analyzed involve 11 patients who were operated on in the above-mentioned method for cancer of the head and/or neck. The individual diagnoses are indicated in Table 1. Some of these patients (three) underwent a second radical dissection on the opposite side of the neck because of recurrence or of incomplete removal of the cancerous tissue at the time of the first procedure. It is obvious that a bilateral neck dissection, irregardless of the interval between procedures, causes a much greater upset in the venous drainage from the head than does a unilateral procedure. There appears to be no uniformity of opinion regarding the interval which should elapse between the two procedures; although this interval will depend on the existing local and general factors, a period of three to four weeks is desirable.[1b] The interval between operations in this group varied from six months to two years.

Bilateral excision of the jugular veins creates a physiologic condition simulating a permanent Queckenstedt sign. In this situation there is a damming of the venous outflow from within the skull, with resultant increased intracranial pressure.[2] In some instances the intracranial pressure is increased twofold.[3] Associated with these intracranial changes, there are evidences of decompensation of the extracranial

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Surgical Resident, Research and Educational Hospitals.

1. (*a*) Lahey, F. H.: Radical Dissection of the Neck, S. Clin. North America **29**(No. 3): 613-640 (June) 1949. (*b*) Gius, J. A., and Grier, D. H.: Venous Adaption After Radical Neck Dissection, Surgery **26**(No. 2):305-320 (Aug.) 1950. (*c*) Slaughter, D.: Personal communication to the author.

2. Ecker, A. D.; Ayer, W. D., and O'Conner, F. J.: Increased Cerebrospinal Fluid Pressure Attributed to Venous Obstruction: Beneficial Effect of Upright Posture, J. A. M. A. **114**:1440-1442 (April 13) 1940.

3. Arid, R. B.: Prolonged Jugular Compression: Diagnostic Test of Neurologic Value, Arch. Neurol. & Psychiat. **45**:633-648 (April) 1941.

venous circulation, such as edema, cyanosis and dilatation of the superficial veins of the face. The severity and permanency of such changes, both intracranial and extracranial, are dependent on the number and size of the existing anastomoses and collaterals.[4]

The venous system of the head is a complex network of abundant communications. The intracranial and extracranial portions communicate freely through the emissary and diploic veins, the large venous plexuses on both sides of the base of the skull, the veins of the orbits and the veins of the neural and arterial foramens. The jugular bulbs are direct extensions of the lateral dural venous sinuses and are the largest channels for venous outflow from the cranial cavity. The straight sinus drains the blood from the choroid plexus and the lateral ventricles, while the longitudinal sinus drains the cerebral cortex. Ordinarily, the lateral sinus of the opposite side can take care of the extra volume of blood if one lateral sinus is thrombosed or if one internal jugular vein is absent after a unilateral neck dissection. However, anatomical variations are common, and if there is not adequate cross circulation at the torcular herophili or if the unobstructed lateral sinus is small, there is a resultant back pressure and increased intracranial pressure.

TABLE 1.—*Data on Eleven Patients Who Underwent Radical Neck Dissection*

Patient	Disease	Operation
J. D.	Squamous cell carcinoma of face	Unilateral radical neck dissection with hemimandibulectomy
W. F.	Epidermoid carcinoma of lip	
T. N.*	Carcinoma of larynx	Unilateral radical neck dissection with hemimandibulectomy
L. K.*	Epidermoid carcinoma of lip	
S. J.	Epidermoid carcinoma of tongue	
G. P.*	Carcinoma of tongue	Unilateral radical neck dissection with hemimandibulectomy
R. B.	Epidermoid carcinoma of face	
F. F.	Epidermoid carcinoma of lip	Unilateral radical neck dissection with hemimandibulectomy
J. D.	Epidermoid carcinoma of lip	Unilateral radical neck dissection
W. C.	Carcinoma of parotid gland	
F. R.	Lymphosarcoma of cervical lymph nodes	

* Patient had undergone previous unilateral radical neck dissection.

In addition to the internal and external jugular veins, other channels through the neck are (1) the collecting veins of the posterior cervical region, (2) the occipital, (3) the profunda cervicis, (4) the posterior jugular, (5) the vertebral, (6) the pharyngeal, (7) the pterygoid, (8) the esophageal, and (9) the vertebral venous plexus. The most important of these is the vertebral venous plexus. This system extends from the cranium to the coccyx, and its importance as a major by-pass has been pointed out by Batson.[5] It becomes eminently important when one or both jugular venous systems are absent. Batson has estimated that the total cross sectional area of this system exceeds that of the two jugular veins, and it is probable that the vertebral venous plexus is sufficient to provide for the entire drainage of blood from the cranial cavity.[5] Studies have been made on patients after ligation of one or both internal jugular veins for lateral or sigmoid sinus

4. Veal, J. R.: The Mode of Development of Collateral Venous Circulation in the Extremities, Am. Heart J. **19**:275-282 (March) 1940.

5. Batson, D. V.: Anatomic Problems Concerned in the Study of Blood Flow, Federation Proc. **4**:139-144 (Sept.) 1944.

thrombosis,[6] but in these cases a different physiological adjustment occurs because high ligation does not impair the collateral channels anastomosing with the jugular vein below the point of ligation. Postoperative complications are relatively infrequent and transitory after the latter procedure, which is not the case after jugular vein removal.

METHOD

On admission to the hospital, all patients were subjected to the usual physical examination, laboratory determinations and procedures necessary to establish accurately the diagnosis in each case. In addition, attempts were made to rule out the presence of any intracranial disease, and a spinal puncture was done to establish a reference point in each patient.

After operation, as soon as the patient's condition warranted it, lumbar punctures were done at definite intervals and continued throughout the postoperative period for various lengths of time. The procedures were accompanied with ophthalmoscopic visualization of the fundi.

TABLE 2.—*Intracranial Pressures Before and After Operation*

Patient	Preoperative Intracranial Pressure, Mm.	After Operation							
		½ Hr.	2 Hr.	4 Hr.	8 Hr.	16 Hr.	4 Days	8 Days	12 Days
J. D.	140	460	452	425	400	384	320	Pt.	Died
W. F.	122	...	415	385	360	350	300	Pt.	Died
T. N.*	104	...	490	490	420	400	350	280	292
L. K.*	110	550	520	510	520	460	380	300	295
S. J.	110	...	335	310	315	284	250	225	220
G. P.*	108	...	480	492	480	465	445	360	335
R. S.	125	415	410	355	362	255	247	210	205
F. F.	120	...	322	325	310	265	234	195	192
J. D.	135	285	282	276	235	242	234	210	206
W. C.	102	300	292	242	251	234	228	225	221
F. R.	95	280	275	302	235	215	215	180	182

* Patient had previously undergone radical dissection on the opposite side.

RESULTS

As indicated in Table 2, the preoperative intracranial pressures, as manifested by lumbar puncture, were well within normal limits in all patients.[7] In six of the 11 cases studied the first postoperative lumbar puncture was done within half an hour after the operation, and with the exception of the first and second patients, who died on the fifth and fourth postoperative days respectively, lumbar punctures were done as late as the 12th day postoperatively.

In three patients in whom the second internal jugular vein was removed, the intracranial pressure was much higher postoperatively than in any of the remaining patients, in whom only a unilateral procedure was done. The intracranial pressure remained consistently higher in the former group throughout the postoperative period and at the time of discharge from the hospital. The intracranial pressure in the first and second patients was generally higher than that in the other patients also undergoing unilateral procedures because prophylactic measures to prevent the increase of intracranial pressure were not undertaken initially.

6. Evans, M. G.: Bilateral Jugular Ligation Following Suppurative Mastoiditis, Ann. Otol. Rhin. & Laryng. **51**:615-625 (Sept.) 1942.

7. Monrad-Khron, G. H.: Clinical Examination of the Nervous System, ed. 9, New York. Paul B. Hoeber, Inc., 1949.

The ophthalmoscopic findings consisted in retinal venous engorgement and blurring of the disk edges. No overt papilledema was observed in any of the patients.

All the postoperative intracranial pressure values were necessarily influenced by the type of dressing applied to the operative site. This usually consisted of four layers: (1) sterile 4 by 4 in. (10 by 10 cm.) gauze over the edges of the incision and skin flaps, (2) "fluffs" or mechanic's waste, (3) a 5-yd. (457 cm.) gauze roll, and (4) an ace bandage. The dressing is applied in a circular manner around the neck from immediately beneath the chin to the base of the neck. It is usually made fairly snug to insure hemostasis of the skin flaps. A dressing applied in this manner compresses the jugular vein on the side not operated on, which further aggravates the impaired venous return from the head and consequently raises the intracranial pressure.

COMMENT

The increase in intracranial pressure following this type of surgery undoubtedly complicates the postoperative course. The usual manifestations of increased intracranial pressure, such as an increase in blood pressure, a decrease in the pulse rate, a decrease in the respiratory rate, and stupor,[8] occurred to some extent in all patients, but these alterations were difficult to evaluate properly because of the blood loss and the anesthetic effects incurred during the course of the operation.

After the presence of increased intracranial pressure was established, various methods were tried in an attempt to counteract the abnormality.

1. Removal of cerebrospinal fluid causes a temporary decrease in the intracranial pressure, but this method is dangerous in the presence of increased intracranial pressure and does not attack the primary problem that exists in these patients, which is a disequilibrium between the blood entering the head and the blood leaving it.[9]

2. Placing the patient in a sitting position with the head higher than the rest of the body aids venous drainage through the remaining venous collateral channels.[9] It has also been shown that an elevation of the head of only 20 degrees from the horizontal position causes a decrease in the mean carotid pressure of 15 mm. of mercury.[10]

3. Protecting the remaining jugular vein from compression by placing some less compressible material parallel to the course of the remaining jugular vein and creating a "tunnel" beneath the circular dressing aids materially in preventing venous congestion.

4. In three patients, 50 cc. of 50% hypertonic solution of glucose was given intravenously to combat cerebral edema because of their poor postoperative state. The results were striking, and the patients rallied quickly. Even though this method of

8. Meyers, B.: Systemic Vascular and Respiratory Effects of Experimentally Induced Alterations in Intraventricular Pressure, J. Neuropath. & Exper. Neurol. **1**:241-264 (July) 1942.

9. O'Connell, J. O.: Vascular Factor in Intracranial Pressure and Maintenance of Cerebrospinal Fluid Circulation, Brain **66**:204-288 (Sept.) 1943. Ecker, Ayer and O'Connor.[2]

10. Shenkin, H. A., and Scheuerman, W. G.: Effects of Changes of Position Upon the Cerebral Circulation in Man, Am. J. M. Sc. **6**:216-224 (Dec.) 1948. Forbes, H. S.: Physiologic Regulation of Circulation, Arch. Neurol. & Psychiat. **42**:804-818 (April) 1940.

decreasing the intracranial pressure is only transitory, it enabled the patients to pass through the most critical phase of the postoperative period in a much safer and more comfortable state.

The methods enumerated above were applied to nine of the 11 patients in this series. Though two patients can hardly be considered a control group, it is apparent from Table 2 that the intracranial pressure was considerably lower in all the treated patients. The two untreated patients died on the fifth and fourth postoperative days, respectively. Autopsy revealed thrombosis of the sigmoid sinus on the side operated on, with moderate cerebral edema (J. D.) and thrombosis of the anterior choroidal artery together with infarction on the side opposite the operation and generalized cerebral edema (W. F.). The exact correlation between the pathological findings in these two cases and the imbalance of cerebral circulation occurring after operations of this type are the subject of another forthcoming paper and will not be discussed here.

That venous adaption does eventually occur, with a resulting normal intracranial pressure, is indicated by the preoperative lumbar puncture pressures in the patients who already had undergone unilateral radical neck dissections, which were normal in all instances.

The problem that exists, therefore, is to combat the severe imbalance in cranial circulation that exists during the immediate postoperative period when the patient is taxed to the utmost by the other usual postoperative stresses.

SUMMARY

A definite increase in intracranial pressure occurs after radical operations on the neck in which the internal jugular vein is removed. This alteration is more pronounced and persistent in patients subjected to removal of the second internal jugular vein. Various methods were used to combat this increased cranial pressure. Repeated lumbar punctures are dangerous in the presence of increased intracranial pressure and do not correct the basic physiologic maladjustment that is present. Placing the patient in a sitting position immediately after operation and protecting the jugular vein on the side not operated on from compression aid markedly in relieving intracranial venous congestion. Hypertonic solution of dextrose was also used intravenously in three patients to reduce the increased intracranial pressure during the most critical period of their convalescence.

EXPERIMENTAL ARTIFICIAL LEFT HEART FOR EXPOSURE OF THE MITRAL AREA

ADRIAN KANTROWITZ, M.D.
ELLIOTT HURWITT, M.D.
AND
ARTHUR KANTROWITZ, Ph.D.
NEW YORK

SINCE the early successes of Gibbon [1] in the maintenance of an artificial circulation in experimental animals, it has been generally recognized that such a system when perfected would be of tremendous value in human intracardiac surgery. Until recently, the workers in this field (Stokes and Gibbon,[2] Björk,[3] Crafoord,[4] Jongbloed,[5] Dennis [6] and others) have concentrated their efforts on the development of an artificial system which would temporarily relieve the entire heart and lungs of their function. Such systems would have a broad field of application. Conditions of the heart and great vessels such as acquired and congenital valvular deformities, septal defects, and abnormalities of the pulmonary arteries would be amenable to a direct visual approach. An artificial heart-lung system might also be used as an emergency procedure to tide a patient over a serious cardiopulmonary crisis.

All these workers have been able to maintain the life of experimental animals temporarily while the circulation was either partially or totally bypassed from their heart and lungs. All of them, however, report that most of their difficulties lie in attempting to reproduce the physiology of the lungs.

Presented in part in the Forum on Fundamental Surgical Problems, Thirty-Sixth Annual Congress of the American College of Surgeons, Boston, Oct. 23, 1950.

From the Surgical and Laboratory Divisions, (Dr. Adrian Kantrowitz, Resident, Surgical Service; Dr. Hurwitt, Chief of the Surgical Division) Montefiore Hospital, New York and the Graduate School of Aeronautical Engineering, (Dr. Arthur Kantrowitz, Professor) Cornell University, Ithaca, N. Y.

1. Gibbon, J. H., Jr.: Artificial Maintenance of Circulation During Experimental Occlusion of the Pulmonary Artery, Arch. Surg. **34**:1105 (June) 1937.

2. Stokes, T. L., and Gibbon, J. H., Jr.: Experimental Maintenance of Life by a Mechanical Heart and Lung During Occlusion of the Venae Cavae Followed by Survival, Surg., Gynec. & Obst. **91**:138, 1950.

3. Björk, V. O.: Brain Perfusions in Dogs with Artificially Oxygenated Blood, Acta chir. scandinav. **96**: (Supp. 137):1, 1948.

4. Crafoord, C.: Some Aspects of the Development of Intrathoracic Surgery, Surg., Gynec. & Obst. **89**:629, 1949.

5. Jongbloed, J.: The Mechanical Heart-Lung System, Surg., Gynec. & Obst. **89**:684, 1949.

6. Dennis, C.: Artificial Maintenance of the Circulation, read before the Symposium on Cardiovascular Research, United States Public Health Service, Washington, Jan. 21, 1950.

For the problem of mitral surgery, only the mitral area need be rendered bloodless. In a previous communication [7] some of us have reported a method of accomplishing this making use of the animal's own lungs. Our system consists essentially in a method of delivering normally oxygenated blood from the left lung into a glass chamber and then pumping it into the arterial tree via the femoral arteries, while at the same time blood from the right lung is prevented from entering the left heart by temporarily occluding the right pulmonary artery with a tourniquet (Fig. 1).

Recently, Sirak and others [8] reported a somewhat different method of accomplishing a similar result. Their method employs a diaphragm at the mitral annulus to shunt the blood from the mitral area and the left ventricle. This method, however, commits one to approaching the mitral area from the ventricle.

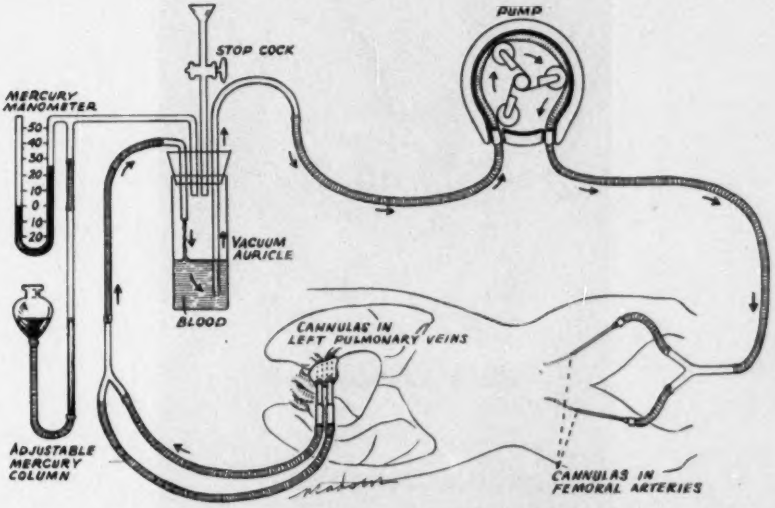

Fig. 1.—Diagram of extracorporeal circuit. Arrows indicate direction of blood flow. (Kantrowitz, A., and Kantrowitz, A.: Proc. Soc. Exper. Biol. & Med. **74**:193, 1950.)

Although Cutler, Levine and Beck [9] in 1924, Pribram [10] in 1925, and Smithy [11] in 1947 attempted mitral surgery with this approach, it appears that the more successful clinical attempts have been made transauricularly. Thus, Cutler and

7. Kantrowitz, A., and Kantrowitz, A.: Experimental Artificial Left Heart to Permit Surgical Exposure of Mitral Valve in Cats, Proc. Soc. Exper. Biol. & Med. **74**:193, 1950.

8. Sirak, H. D.; Ellison, E. H., and Zollinger, R. M.: Cardiotomy into an Empty Left Ventricle, Surgery **28**:225, 1950.

9. Cutler, E. C.; Levine, S. A., and Beck, C. S.: The Surgical Treatment of Mitral Stenosis: Experimental and Clinical Studies, Arch. Surg. **9**:689 (Nov.) 1924.

10. Pribram, B. O.: Die operative Behandlung den Mitralstenose, Arch. klin. Chir. **142**:458, 1926.

11. Smithy, H. G.: An Approach to the Surgical Treatment of Chronic Valvular Disease of the Heart, read before the Sixteenth Annual Assembly of the Southeastern Surgical Congress, Hollywood, Florida, April, 1948.

Levine [12] in 1923, Allen and Graham [13] in 1922, Souttar [14] in 1925, Smithy [11] in 1947, Harken and others [15] in 1947, and Glover, O'Neill and Bailey [16] in 1949 all approached the mitral valve from its auricular side. Experimentally, Templeton and Gibbon [17] reported their reconstruction of cardiac valves, again using the auricle as the avenue of approach.

Therefore, while procedures have yet to be developed for the ultimate surgical treatment of mitral stenosis, it would seem desirable from the experimental point of view to have access to the mitral valve from both the auricular and the ventricular side.

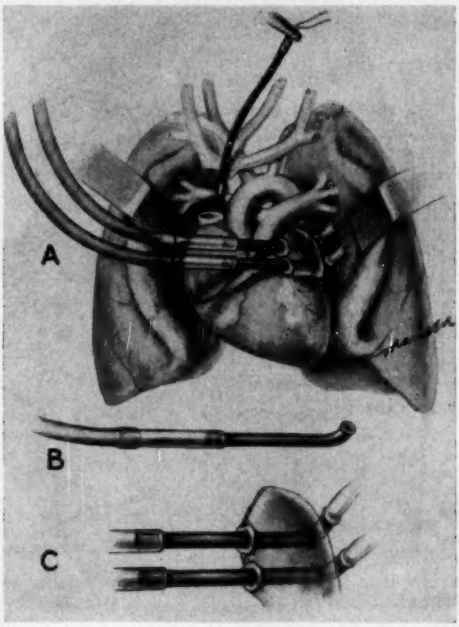

Fig. 2.—*A*, illustration of cannulas in place in left pulmonary veins and tourniquet occluding right pulmonary artery. *B*, one pulmonary vein cannula. *C*, cannulas passing through left auricular appendage and auricle and fixed into the left pulmonary veins. (Proc. Soc. Exper. Biol. & Med. **74**:193, 1950.)

12. Cutler, E. C., and Levine, S. A.: Cardiotomy and Valvulotomy for Mitral Stenosis, Boston M. & S. J. **188**:1023, 1923.

13. Allen, D. S., and Graham, E. A.: Intracardiac Surgery: New Method, J. A. M. A. **79**:1028 (Sept. 23) 1922.

14. Souttar, P. W.: The Surgical Treatment of Mitral Stenosis, Brit. M. J. **2**:603, 1925.

15. Harken, D. E.; Ellis, L. B.; Ware, P. F., and Norman, L. R.: The Surgical Treatment of Mitral Stenosis, New England J. Med. **239**:802, 1948.

16. Glover, R. P.; O'Neill, T. J. E., and Bailey, C. P.: Commissurotomy for Mitral Stenosis, Circulation **1**:329, 1950.

17. Templeton, J. Y., III, and Gibbon, J. H., Jr.: Experimental Reconstruction of Cardiac Valves by Venous and Pericardial Grafts, Ann. Surg. **129**:161, 1949.

Recently, also, there have been several reports of systems which bypass portions of the heart. These systems, although not directly intended for mitral surgery, are of significance in the general development of this field. Sewell and Glenn [18] described their successful bypassing of the right auricle and ventricle. They were able to cannulate the venae cavae and shunt this venous blood into the pulmonary artery. Wesolowski and others [19] reported a method of successfully bypassing the left ventricle by cannulating the auricular appendage and using a normally sealed mitral valve to keep the auricle a closed chamber.

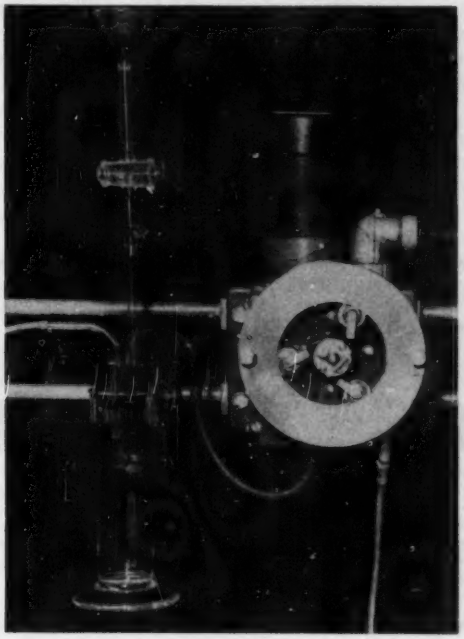

Fig. 3.—Photograph of vacuum auricle and pump. (Proc. Soc. Exper. Biol. & Med. **74**:193, 1950.)

APPARATUS

The apparatus used in our method consists of four main elements (Figs. 2 and 3). The first is stainless steel cannulas for the left pulmonary veins. The second is a closed glass chamber to act as the auricular reservoir. This chamber has four openings, each admitting a glass tube. The first tube delivers the blood collected from the left lung. The second tube to the bottom of the chamber collects the blood

18. Sewell, W. H., Jr., and Glenn, W. W. L.: Experimental Cardiac Surgery, Surgery **28**:474, 1950.

19. Wesolowski, S. A.; Miller, H. H.; Halkett, J. A. E., and Welch, C. S.: Experimental Replacement of the Heart by a Mechanical Extracorporeal Pump, Bull. New England M. Center **12**:41, 1950.

and carries it to the pump. The third tube, with a stopcock and funnel, permitting the system to be closed or opened to atmospheric pressure, allows for the addition of fluids. The fourth tube is connected to an adjustable mercury column whose height alters the pressure in the vacuum auricle, which can then be read on an attached mercury manometer. The third element is a modified roller-type pump such as has been used by DeBakey [20] and Gibbon.[21] The position of the rollers is controlled by having them ride on completely circular tracks, held there by phosphor bronze leaf springs. The lumen is controlled by shims and thus can be varied precisely by changing the total shim thickness. The creeping of the rubber tube due to the rolling action is prevented by the use of rubber cuffs cemented to the outside of the rubber tube. The fourth element is latex rubber tubing connecting all the above-described elements. All the equipment in contact with blood is silicone-coated with General Electric Dri-Film No. 9987.

TECHNICAL PROBLEMS

The input side of the pump created surges of negative pressure which drew the blood irregularly from the pulmonary veins and tended to collapse them suddenly, thus sealing the openings of the cannulas. This was overcome by introducing an

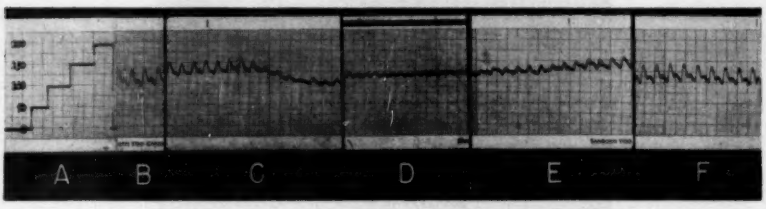

Fig. 4.—Sections of continuous blood pressure tracings in left subclavian artery of Cat 59, made with a Sanborn electromanometer and electrocardiograph. *A*, calibration in millimeters of mercury. *B*, before introduction of cannulas. *C*, animal's left heart and artificial system in operation simultaneously. Latter portion, occlusion of right pulmonary artery with subsequent elimination of animal's left heart. *D*, animal completely maintained on artificial system. *E*, change-over from artificial system to both left heart and artificial system. *F*, conclusion of experiment. (Proc. Soc. Exper. Biol. & Med. **74**:193, 1950.)

air chamber (the artificial auricle) between the cannulas and the pump and by designing the cannulas so that they could be aligned with the walls of the vessels.

The blood flow, slowed by resistance during its passage through the input tubes, was accelerated by reducing the pressure in the artificial auricle to between —20 and —30 mm. of mercury. In addition, at this range of negative pressure, the system was found to be most stable.

Hemolysis, which might have been anticipated because of the rapid circulation of blood in large quantities through an artificial system, was not a problem in our technic. When the equipment was coated with silicone and the pump designed so that the walls of the rubber tubing never wholly collapsed when compressed by

20. DeBakey, M. E.: Simple Continuous Flow Blood Transfusion Instrument, New Orleans M. & S. J. **87**:386, 1934.

21. Gibbon, J. H., Jr.: The Maintenance of Life During Experimental Occlusion of the Pulmonary Artery Followed by Survival, Surg., Gynec. & Obst. **69**:602, 1939.

the roller, thus minimizing crushing and shearing of red cells, hemolysis became insignificant. Tests for hemolysis in which one unit of citrated human bank blood was circulated through the artificial system at the rapid rate of 500 cc. per minute for one hour revealed only faint traces of hemoglobin in the plasma. Although no measurements of the oxygen saturation were made, arterial blood always appeared to be bright red. Experience with pneumonectomies has shown that man and other animals survive indefinitely with one lung removed. It is still to be established whether a human being suffering from long-standing mitral stenosis can safely oxygenate all his blood on one lung for a period long enough to permit an intracardiac operation. It can be seen from Figure 4 that the blood pressure with the artificial system is essentially a mean pressure, reflecting the surges inherent in the pump whose output is otherwise nonpulsatile. While others [22] have reported that pulsatile flow is necessary for the normal functioning of organs, it has been our experience that not only is an essentially nonpulsatile flow at approximately normal mean pressures, for periods up to one-half hour, consistent with the animal's survival but that there are no observable harmful effects.

OPERATIVE TECHNIC

The technic used is as follows: The animal is anesthetized intravenously with 2.5% thiopental sodium (pentothal®). The right and left femoral arteries are exposed for the insertion of cannulas. The chest is opened by splitting the sternum, and both pleural cavities are entered. An artificial respirator attached to an endotracheal tube maintains the respiration with atmospheric air. The right pulmonary artery is dissected free. A silk ligature is passed around it and allowed to lie loosely in place. The left pulmonary veins are dissected free. Elastic threads are passed around them and allowed to lie loosely in place. After heparinization of the animal, cannulas directed cephalad are fixed in both femoral arteries. The pulmonary vein cannulas are then passed through the left auricular appendage and the chamber of the left auricle into the openings of the left pulmonary veins. They are fixed in this position with the previously placed elastic threads. The artificial system, previously filled with blood from a donor animal, is started. By lowering the mercury column, the pressure in the vacuum auricle is now adjusted to a negative pressure of —25 mm. of mercury. The circulation is maintained for approximately one minute with the animal's left heart and the artificial system in operation simultaneously; the blood coming from the right lung still passes through the left side of the animal's own heart while the blood coming from the left lung is collected by the cannulas and delivered via the artificial system to the aorta. By the end of this time, the previously placed silk ligature tourniquet (Fig. 2*A*) around the right pulmonary artery is gradually tightened, occluding this vessel. Thus, all the blood henceforth is shunted through the left lung and the artificial system. At this point, either the left auricle or the left ventricle is opened. The steps to discontinue the artificial and restore the normal circulation are now begun. The exploratory incision in the auricle or ventricle is closed. The tourniquet around the right pulmonary artery is gradually released, allowing blood to pass through the right lung and return to the animal's left auricle. The elastic ligatures around the cannulas in the pulmonary

22. Jongbloed.[5] Gesell, R. A.: On the Relations of Pulse Pressure to Renal Secretion, Am. J. Physiol. **32**:70, 1913. Hooker, D. R.: A Study of the Isolated Kidney: Influence of Pulse Pressure upon Renal Function, Am. J. Physiol. **27**:24, 1910.

veins are cut and the cannulas withdrawn from the veins into the animal's left auricular chamber. The pump is stopped and the cannulas removed by withdrawing them until their tips are in the auricular appendage and by ligating the appendage. Protamine sulfate is administered intravenously to counteract the previously administered heparin. The paricardium is loosely reapproximated and the chest wound closed in layers. The cannulas are removed from the femoral arteries and these vessels ligated.

RESULTS

A total of 61 cats were used in this series. The first 53 were lost in the process of developing the final technic. Of the last eight animals, all recovered from the procedure and survived for periods exceeding 36 hr., except for one which was immediately killed to obtain data. Four died in periods ranging from 36 to 54 hr. postoperatively. One animal (on the artificial system 34 min.) died suddenly after surviving seven months in apparently good health and was discarded by mistake before a postmortem examination could be performed. Two animals which are living to the date of this writing (a period of nine months) appear to enjoy normal health (Table 1). In the last 25 experiments, either the left auricle or the left ventricle

Results of Experiments After the Development of the Technic

Cat No.	Minutes on Artificial Left Heart	Date of Experiment	Time Survived	Autopsy Findings
54	28	12/14/49	36 hr.	Mucus plug in trachea
55	15	12/17/49	48 hr.	Empyema, bilateral lobar pneumonia
56*	14	12/19/49	.....	.....
57	40	12/20/49	46 hr.	Meningitis
58	29	12/24/49	54 hr.	Tracheobronchial tree blocked by thick secretions
59	40	12/27/49	0	Killed immediately after procedure; no abnormal findings
60*	32	12/29/49	.....	.....
61	34	2/18/50	7 mo.	Animal discarded by mistake

* Alive and well at this writing, a period of nine months.

was opened in every case while the circulation was maintained by the artificial system and in every instance found to be practically bloodless.

Direct blood pressure readings from the left subclavian artery revealed that the mean pressure rarely fell below 100 mm. of mercury during the entire procedure, including the period on the artificial heart.

We have begun experiments using this procedure in dogs. While as a whole the method seems applicable, several modifications have been made. In dogs, there are three pulmonary veins from each lung (contrasted with two in cats) opening separately into the left auricle. Therefore, in order to collect all the blood from the left lung, three cannulas had to be passed. Further, it was found easier to pass the ligature around the right pulmonary artery (to act as the tourniquet) intrapericardially rather than extrapericardially.

An insufficient number of experiments have been done in dogs to yield significant data concerning survival rates. However, two dogs have survived the immediate postoperative period. One of these animals was on the artificial heart for 37 min. and survived for 29 days. During this period the animal did not appear well and refused food. Postmortem examination revealed diffuse bilateral bronchopneumonia.

A second dog was maintained on the artificial left heart for 16 min. He completely recovered from the procedure and appeared to be enjoying good health. He died on the 25th postoperative day. Postmortem examination revealed moderate bilateral pleural effusion and bilateral bronchopneumonia.

SUMMARY

A system of bypassing the left auricle and ventricle to expose the mitral area for surgical intervention is described. It differs from other reported extracorporeal systems in that it makes use of the animal's own lung and allows for either a transauricular or a transventricular surgical approach to the mitral valve.

The system consists of delivering normally oxygenated blood from the left lung, via cannulas in the pulmonary veins, into a glass chamber and thence pumping it into the aorta via the femoral arteries, while blood from the right lung is temporarily prevented from entering the left heart. Blood pressures are always maintained at adequate levels, and hemolysis is insignificant.

In the eight experiments after the development of the final technic, one cat was immediately killed to obtain data, four survived for 36 to 54 hr., one survived for seven months, and two are alive and well at this writing (a period of nine months). In preliminary experiments with dogs, two animals have survived beyond the immediate postoperative period.

POSTCHOLECYSTECTOMY COMPLICATIONS DUE TO INCOMPLETE REMOVAL OF GALLBLADDER AND CYSTIC DUCT

Report of a Case of So-Called Reformed Gallbladder

WILLIAM B. A. J. BAUER, M.D.
LADYSMITH, WIS.

MANY case reports of so-called reformed gallbladder have been described in the literature.[1] An enormous amount of work has been done by Hicken and his associates, whose reports are both thorough and convincing. Therefore, the chief value of presenting this case is from the standpoint of adding weight to the mounting opinion that such cases occur all too frequently. Secondly, I feel it is rather unusual, yet reasonable, that in this case the diagnosis was proved preoperatively by oral ingestion of iodoalphionic acid (priodax®). As far as I can determine, the diagnosis in previously reported cases was made by means of exploratory laparotomy, with or without cholangiography. Since this report was written, Dr. Michael Weingarten, of New York, reported a case with preoperative visualization in *The Journal of the American Medical Association,* Jan. 20, 1951.[2]

The pathological report was made by Dr. Etheldred Shafer, Jackson Clinic, and the x-ray report by Dr. Donald deForest Bauer, Minneapolis.

1. Hicken, N. F.; White, L. B., and Coray, Q. B.: Incomplete Removal of Cystic Duct as a Factor in Producing Postcholecystectomy Complications, Surgery **21**:309-320 (March) 1947. Hicken, N. F.; Stevenson, V. L.; Allen, L. M., and Cornwall, C. R.: Double Gall Bladders, ibid. **25**:431-440 (March) 1949. Hicken, N. F.; McAllister, J. A.; Franz, B., and Crowder, E.: Technic, Indications and Value of Postoperative Cholangiography, Arch. Surg. **60**:1102-1113 (June) 1950. Best, R. R., and Hicken, N. F.: Technique of Immediate Cholangiography, Surg., Gynec. & Obst. **65**:217-219 (Aug.) 1937. Hicken, N. F.; Coray, Q. B., and Orem, J. F.: Postoperative Cholangiography, Rocky Mountain M. J. **38**:709-713 (Sept.) 1941. Hicken, N. F.; Coray, Q. B., and Franz, B.: Anatomic Variations of the Extrahepatic Biliary System as Seen by Cholangiographic Studies, Surg., Gynec. & Obst. **88**:577-584 (May) 1949. Best, R. R., and Hicken, N. F.: The Therapeutic Value of Glyceral Trinitrate in Biliary Colic and in Postoperative Phase of Biliary Tract Disease, Am. J. Surg. **39**:533-537 (March) 1938. Hicken, N. F., and Best, R. R.: Cholangiography: The Visualization of the Gallbladder and Bile Ducts During and After Operations, Ann. Surg. **103**:210-229 (Feb.) 1936. Hunt, H. B.; Hicken, N. F., and Best, R. R.: Exploration of the Biliary Ducts by Cholangiography During and Following Operations, Am. J. Roentgenol. **38**:542-563 (Oct.) 1937. Hicken, N. F.; Stevenson, V. L.; Franz, B., and Crowder, E.: The Technic of Operative Cholangiography, Am. J. Surg. **78**:347-355 (Sept.) 1949. Partington, P. F., and Sachs, M. D.: Routine Operative Cholangiography, pamphlet from Department of Surgery and Department of Radiology, Western Reserve University School of Medicine, Cleveland, 1948. Walters, W., and Snell, A. N.: Diseases of Gall Bladder and Bile Ducts, Philadelphia, W. B. Saunders Company, 1940. Walters, W., and Thiessen, N. W.: Visual Method of Studying the Physiology of the Common Bile Duct, Proc. Staff Meet., Mayo Clin. **9**:772-775 (Dec.) 1934. Hicken, N. F.; White, L. B., and Coray, Q. B.: External Biliary Fistulas, Surg. Gynec. & Obst. **74**:828-835 (April) 1942.

2. Weingarten, M.: Calculi in Dilated Stump of Cystic Duct: Preoperative Visualization, J. A. M. A. **145**:157-159 (Jan. 20) 1951.

REPORT OF A CASE

The patient, a housewife 44 yr. of age, had undergone a cholecystectomy in May 1943. The gallbladder contained multiple small stones. After this first operation she had been well for four years. She now complained of "gas attacks," general indigestion, and indefinite intermittent right upper quadrant pain of two years' duration. The use of antispasmodics and reassurance did not relieve her. Her bouts increased in frequency and severity.

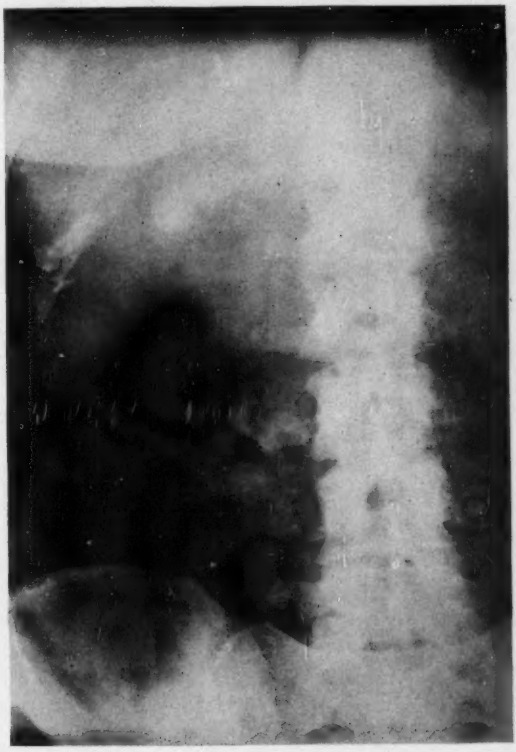

Fig. 1.—Preoperative roentgenogram taken after priodax® was given.

It became increasingly obvious that further investigation was necessary. Attacks became more frequent and severe, although at no time were they truly agonizing. At this time, January 1950, priodax® cholecystography was attempted.

X-Ray Report.—The first attempt at cholecystography was made in the routine manner; 6 priodax® tablets were given after a fat-free supper and roentgenographic exposure made about 16 hr. later. This revealed a round, faint density 1.25 cm. in diameter, about 5 cm. to the right of the body of the second lumbar vertebra. A double dose of priodax® a few days later again revealed a density in the same place but now considerably more intense and 3 to 4 mm. greater in diameter. It was the shape of a comma lying on its left side. A repeat roentgenogram 90 min. after a fatty meal revealed merely the faintest outline of the "comma." These findings were interpreted as conclusive evidence of postcholecystectomy functioning gallbladder tissue.

With no history of jaundice and no direct evidence of acholic stools, it had been difficult to establish a diagnosis of choledochal stone. The literature reveals several cases of double gallbladders with separate as well as Y-shaped cystic ducts. There also are on record cases of postoperative kinking of the common duct by direct adhesions as well as adhesions to the proximal incompletely removed cystic duct, with resultant kinking of the choledochus. The cholecystography gave ample evidence of the cause of the difficulty, particularly since the "reformed gallbladder" disappeared after the fatty meal, which had been preceded by an intravenous urogram to rule out renal lithiasis. A barium meal had also been given to rule out

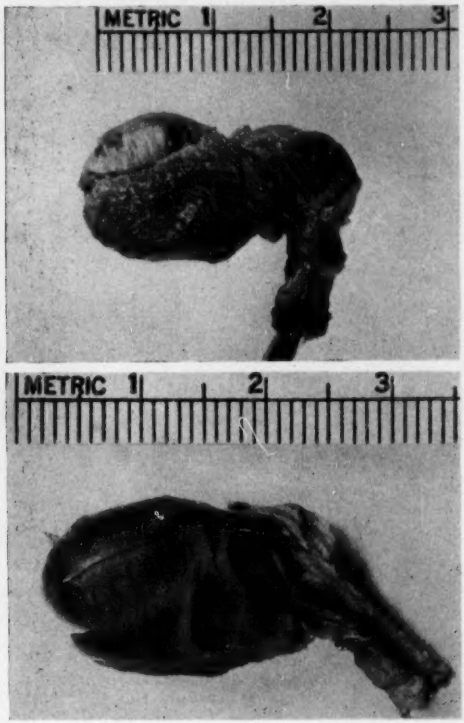

Fig. 2.—Photographs of pathological specimen.

a diverticular pouch of the duodenum. Other laboratory studies were noncontributory, including an amylase test.

Thus, on Feb. 24, 1950, a laparotomy was performed. An upper right paramedian incision was made, exposing the peritoneal cavity. The usual postoperative mass of adhesions was present, extending from the gastrohepatic ligament to the hepatic flexure of the colon. These were separated and freed and the common hepatic duct finally exposed. Also, a short cystic duct with a dilated proximal end (so-called reformed gallbladder) was visualized. At the junction of the cystic duct with the choledochus there was a slight kinking of the latter. It was further seen that this was due to traction of the "reformed gallbladder," the latter being firmly adherent to the liver, but the entire pathologic process was within the relative confines of the gastrohepatic ligament. Further dissection revealed a definite artery to this dilated cystic duct, which was ligated. The cystic duct was ligated close to its junction with the

choledochus, and the whole was removed, as in the usual gallbladder case. These were no stones in the common duct. At the time of operation it was at first difficult to be certain whether I was dealing with a second, entirely separate gallbladder and cystic duct or, as preoperatively agreed on, a so-called reformed gallbladder. My impression, however, was that it was the latter, and this was borne out by the pathological specimen.

Pathological Report.—Gross Changes: The specimen consisted of a saclike structure measuring 2.8 by 1.5 by 1.2 cm. attached to a pedicle measuring approximately 1 cm. in length and up to 0.5 cm. in width. There were hemostat marks along the excised end of the pedicle and across one surface of the sac. The wall was thin and light green and roughened by numerous tiny, fibrous tags. The sac was slightly twisted on itself near the junction with the pedicle. Section revealed approximately 2 ml. of green, viscid bile in the lumen. The sac had a velvety, dark green lining. The proximal twisted portion resembled dilated valves of Heister.

Microscopic Changes: Section showed a thin-walled gallbladder which was lined by plicae of normal appearance. The subepithelial tissue contained a few lymphocytes. The underlying muscularis showed slight fibrosis.

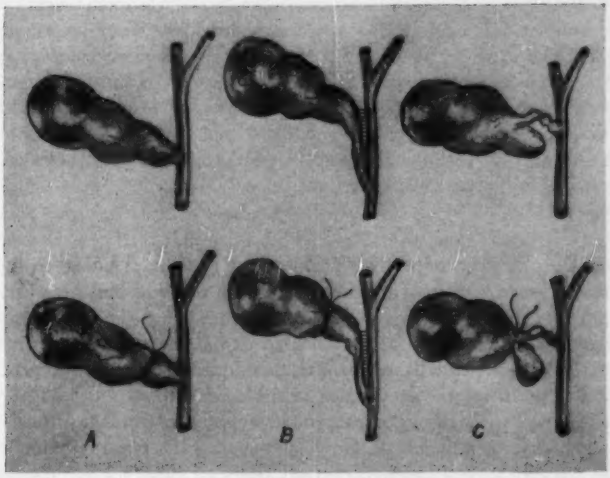

Fig. 3.—Schematic drawings representing a few of the more common anatomic variations of the cystic duct. (Reproduced by permission of Hicken, N. F.; White, L. B., and Coray, Q. B.: Incomplete Removal of Cystic Duct as a Factor in Producing Postcholecystectomy Complications, Surgery **21**:309-320 [March] 1947.)

Pathological Diagnosis.—The diagnosis was chronic cholecystitis of an incompletely removed gallbladder.

CAUSE OF "REFORMED GALLBLADDER" IN THIS CASE

It would seem that this is a case in which originally Hartmann's pouch was tied off with the cystic duct intact and secondary dilatation of the pouch occurred. This is in accordance with one of the causes suggested by Hicken and others, whose drawing is reproduced here. The anatomic variation present is demonstrated as *C* in the drawing.

COMMENT

Statistics reveal a high percentage of postoperative recurrence of symptoms of gallbladder disease or of nonimprovement of symptoms. Experience bears out these statistics. Patients complain of vague abdominal pains, gas and belching. Occa-

sionally, they complain of colicky pain and jaundice. A summary of 1,100 operative cases [3] revealed 75% of the patients free from gallbladder symptoms, 4.5% unimproved, and 20.5% improved but still complaining of vague abdominal pains, belching and gas. In a few of the latter achlorhydria following cholecystectomy has apparently developed and their symptoms are alleviated by the proper dosage of hydrochloric acid. In patients delaying operation too long for economic reasons or through fear of surgical intervention contiguous disease such as pancreatitis and hepatitis may have developed. Cholecystectomy in such cases will not necessarily give completely satisfactory results, even when excellent surgical skill has been used. Occasionally, however, remediable pathologic changes have been missed.

Hepatic duct stones, choledochal stones, and anomalous conditions (such as double gallbladders) confound the most experienced surgeons. "Reformed gallbladders" from cystic duct remnants probably occur oftener than we are aware. Many errors of omission can probably be eliminated by a routine cholangiographic study at the operating table. Properly accomplished and interpreted, this could reduce some of the annoying biliary complications occurring postoperatively.

Apparently there are a few select cases in which priodax® cholecystography can be successfully accomplished. When this drug is properly assimilated (no vomiting or diarrhea) and where there is present a potential unobstructed cavity, lined by sufficient secretory mucosa, such cholecystography appears feasible as an adjunct to the present diagnostic armamentarium.

SUMMARY

Persistent postcholecystectomy symptoms are equally irritating to the patient and to the physician. Thorough reports have been made in the literature. A case is reported here of a "reformed gallbladder" representing the dual complications of a diseased cystic duct and traction kinking. It is interesting that a preoperative diagnosis was clearly established by means of priodax® cholecystography. An explanation is given for the occurrence of the condition.

Cholangiography at the operating table appears to offer the best solution toward minimizing postcholecystectomy symptoms. It appears to me to be as imperative to take a cholangiogram in all cases of biliary tract disease before closure as it is to take a roentgenogram after reduction in all cases of fracture.

3. Jackson, S. A., and Schwei, P. G.: Exhibit on Surgical Treatment of the Gallbladder and Common Bile Ducts, presented at the Wisconsin State Medical Meeting, 1949.

ENDOMETRIOSIS OF THE VERMIFORM APPENDIX

Review of Literature, with Addition of Nine New Instances, One of Which Caused Severe Melena

DONALD C. COLLINS, M.D., M.S. (Path. & Surg.), Sc.D., F.I.C.S.
HOLLYWOOD, CALIF.

ENDOMETRIOSIS means, pathologically, the occurrence of endometrial-like tissue outside the limits of the mucosal lining of the uterus. Endometriosis of the vermiform appendix, although rare, is being seen with increased frequency. This type of appendical lesion may cause grave complications that can threaten the life of the patient, as will be described in a case report in this contribution. Appendical endometriosis is being more frequently recognized because both the pathologist and the surgeon have learned to identify its gross and microscopic characteristics.

Endometriosis was first reported and described by von Rokitansky [1] in 1860. After this discovery, many theories were advanced to explain the occurrence of endometrial lesions in extragenital anatomic locations. These were designated as examples of "external endometriosis." In 1921 Sampson [2] partially clarified this complex problem by proposing his theory of transtubal retrograde endometrial implantation at the time of menstruation. However, because proved instances of endometriosis had been reported by Thompson [3] in the lungs, by Mankin [4] in the left thigh, by Navratil and Kramer [5] in the extensor carpi radialis muscle of the forearm, by Büngeler and Fleury Silveira [6] in the pleural cavity, and, finally, by Schlicke [7] in the posterior aspect of the left thigh, it was agreed that other theories would be required to explain such pathologic phenomena. The celomic metaplasia

Submitted for publication April 24, 1951.

From the Department of Surgery, College of Medical Evangelists, and the Section on General Surgery, Hollywood-Presbyterian Hospital, Los Angeles.

1. von Rokitansky, C.: Über Uterusdrusen-Neubildung in Uterus- und Ovarial-Sarcomen, Ztschr. k. k. Gesselsch. Aerzte Wien **16**:577-581, 1860.

2. Sampson, J. A.: Perforating Hemorrhagic (Chocolate) Cysts of Ovary: Their Importance and Especially Their Relation to Pelvic Adenomas of Endometrial Type (Adenomyoma of the Uterus, Rectovaginal Septum, Sigmoid, etc.), Arch. Surg. **3**:245-323 (Sept.) 1921.

3. Thompson, A. P.: Malignant Endometrioma with Metastases in the Lungs, Proc. Roy. Soc. Med. **19**:16-17, 1926.

4. Mankin, Z. W.: Beiträge zur Lehre von den endometrioiden Heterotopien, Arch. klin. Chir. **175**:314-334, 1933.

5. Navratil, E., and Kramer, A.: Endometriose in der Armmuskulatur, Klin. Wchnschr. **15**:1765-1770 (Nov. 28) 1936.

6. Büngeler, W., and Fleury Silveira, D.: Considerações sobre a patogenia das endometrioses (a proposito de 3 casos de endometriose externa), Arg. cir. clin. e exper. **3**:169-171 (June) 1939.

7. Schlicke, C. P.: Ectopic Endometrial Tissue in the Thigh, J. A. M. A. **132**:445-446 (Oct. 26) 1946.

theory of Iwanoff [8] appears at present to be generally accepted. In its present modified form it may be simply stated as follows: The Müllerian (paramesonephric) duct is derived from the embryonic celomic epithelium and mesenchyma and produces most of the female genital tract, including the endometrium. Other adult derivatives of these embryonic celomic cells may retain the potentiality of forming tissue which is functionally and histologically indistinguishable from endometrial tissue. The metastasis theory, advanced by Halban [9] to explain these distant endometrial lesions located outside of the peritoneal cavity, has been largely abandoned. He advocated that endometrial metastases occurred by way of the lymphatics and blood vessels that drained the uterus. If this theory were correct, one would expect to find frequent endometrial lesions in the lungs. This is not the case. The reader is referred to the splendid review recently contributed by Ranney [10] on the etiology of endometriosis for a further detailed discussion on this fascinating subject.

Pathologically, each endometrial lesion is in reality a miniature uterus with functioning glands and, usually, stroma. Under the influence of ovarian hormones, this tissue responds by going through all the phases of the menstrual cycle, even forming decidua during pregnancy and undergoing atrophy at the menopause. This tissue menstruates. Since endometrium lacks a basement membrane, it easily invades surrounding tissues. Lack of drainage of this menstrual blood away from the lesion produces tarry or "chocolate" cysts that steadily enlarge and may finally rupture, with spillage of their contents and with the production of secondary endometrial implantation. Such spillage usually produces dense and strong fibrous adhesions within the peritoneal cavity. Endometriosis is unique in that it is an invasion of normal tissues by equally benign and normal tissue of a different type. Occasionally, endometriosis terminates in a highly malignant adenocarcinoma.

The Table summarizes the data reported in the literature concerning endometriosis of the vermiform appendix, as presented by 64 authors [11] between the years 1860 and 1951.

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8. Iwanoff, N. S.: Drüsiges cystenhaltiges Uterusfibromyom kompliziert durch Sarcom und Carcinom (Adenofibromyoma Cysticum Sarcomatodes Carcinomatorum), Monatsschr. Geburtsh. u. Gynäk. **7**:295-304, 1898.

9. Halban, J.: Hysteroadenosis metastatica (Die lymphogene Genese der sog. Adenofibromatosis heterotopica), Wien. klin. Wchnschr. **37**:1205-1206 (Nov. 20) 1924.

10. Ranney, B.: Collective Review: Etiology of Endometriosis, Internat. Abstr. Surg. **86**:313-334, 1948; in Surg., Gynec. & Obst., April, 1948.

11. (*a*) Footnotes 1 to 10. (*b*) King, W. W.: The Clinical Symptoms of Pelvic Adenomyomata, Brit. M. J. **2**:573-575 (Sept. 27) 1924. (*c*) Meigs, J. V.: Adenomyomata or Tumors Composed of Endometrial-like Tissue, Boston M. & S. J. **195**:343-347 (Aug. 19) 1926. (*d*) Smith, G. V.: Endometrioma: Clinical and Pathologic Study of 159 Cases Treated at the Clinic of The Free Hospital for Women, Brookline, Massachusetts, Am. J. Obst. & Gynec. **17**:806-814 (June) 1929. (*e*) Keene, F. E., and Kimbrough, R. A.: Endometriosis: Review Based on the Study of 118 Cases, J. A. M. A. **95**:1164-1168 (Oct. 18) 1930. (*f*) Allen, E.: A Clinical and Experimental Study of Endometriosis, Am. J. Obst. & Gynec. **26**:803-814 (Dec.) 1933. (*g*) Moss, T. C.: Endometriosis, Am. J. Clin. Path. **9**:345-352 (May) 1939. (*h*) Sherwood, M. W.: Endometriosis: Pathology, Surgery and After-Treatment, Texas J. Med. **35**:16-19 (May) 1939. (*i*) Philipp, E., and Huber, H.: Die Klinik der Endometriose im Lichte neuer Forschungsergebnisse, Zentralbl. Gynäk. **63**:482-497 (March 4) 1939. (*j*) Payne, F. L.: The Clinical Aspects of Pelvic Endometriosis, Am. J. Obst. & Gynec. **39**:373-382 (March) 1940. (*k*) Fallas, R., and Rosenblum, G.: Endometriosis: Study of 260 Private Cases, ibid. **39**:964-975 (June) 1940. (*l*) Dannreuther, W. T.: The Treatment of Pelvic Endometriosis, ibid. **41**:461-474

Case 133 in this study of 134 cases, and the eighth case in a newly added group of nine cases, is presented in greater detail, because of its unusual clinical features.

REPORT OF A CASE

CASE 133.—Mrs. L. J. B. (C-45340), aged 26 years, a cashier by occupation, was seen in my office on Aug. 29, 1950. She complained of severe lower back pain, followed by profuse rectal bleeding that relieved her symptoms three days prior to her menstrual period. The amount of blood passed per rectum for three days in each month was large and in the form of foul-

(March) 1941. (*m*) Hurd, R. A.: Some Observations on Endometriosis, Am. J. Surg. **53**:61-70 (July) 1941. (*n*) Haydon, G. B.: A Study of 569 Cases of Endometriosis, Am. J. Obst. & Gynec. **43**:704-709 (April) 1942. (*o*) Sturgis, M. C.: Some Clinical Aspects of Peritoneal Endometriosis, M. Woman's J. **49**:295-299 (Oct.) 1942. (*p*) Sanders, R. L.: Endometriosis: Clinical and Therapeutic Considerations; Report of 120 Private Cases, Surgery **13**:224-239 (Feb.) 1943. (*q*) Jenkinson, E. L., and Brown, W. H.: Endometriosis: Study of 117 Cases, with Special Reference to Constricting Lesions of the Rectum and Sigmoid Colon, J. A. M. A. **122**:349-354 (June 5) 1943. (*r*) Masson, J. C.: Present Conception of Endometriosis and Its Treatment, Tr. West. S. A. **53**:35-50, 1945. (*s*) Thierstein, S. T., and Allen, E.: A Comparative Analysis of the Diagnosis and Treatment of Endometriosis, Including a Report of 53 Cases of Intestinal Endometriosis, Am. J. Obst. & Gynec. **51**:635-642 (May) 1946. (*t*) Cotte, G.; Mathieu, J., and Guillemin, G.: 259 cas d'endométriose, Rev. franç. gynéc. et obst. **41**:16-20, 1946. (*u*) Abell, I., and Abell, I., Jr.: Endometriosis, South. Surgeon **13**:321-329 (May) 1947. (*v*) Sutler, M. R.: Endometriosis of the Intestinal Tract, Surgery **22**:801-805 (Nov.) 1947. (*w*) Machado, L. M.: Endometriose do apêndice, Rev. ginec. obst. **1**:70-76 (Jan.) 1948. (*x*) Kelly, F. J., and Schlademan, K. R.: Endometriosis: Its Surgical Significance; Critical Analysis of 179 Cases, Surg., Gynec. & Obst. **88**:230-236 (Feb.) 1949. (*y*) DeSanto, D. A., and McBirnie, J. E.: Endometriosis: Clinical and Pathological Study of 219 Cases, California Med. **71**:274-279 (Oct.) 1949. (*z*) Collins, D. C.: Unusual Lesions of the Vermiform Appendix, Ann. West. Med. & Surg. **3**:384-387 (Nov.) 1949. (*a'*) Lamb, W. K.: Endometriosis, California Med. **72**:113-117 (Feb.) 1950. (*b'*) Colcock, B. P., and Lamphier, T. A.: Endometriosis, Ann. Surg. **131**:507-518 (April) 1950. (*c'*) Scott, R. B., and TeLinde, R. W.: External Endometriosis, the Scourge of the Private Patient, ibid. **131**:697-719 (May) 1950. (*d'*) Hirschberg, A.: Deciduale Zellbildungen am Wurmfortsatz bei Tubenschwangerschaft (Periappendicitis decidualis), Arch. Gynäk. **74**:620-632, 1905. (*e'*) Hueter, C.: Über entzündliche drüsenartige Neubildungen des Peritoneums (Peritonitis adenoides), Frankfurt. Ztschr. Path. **21**:283-296, 1918. (*f'*) Meigs, J. V.: Endometrial Hematomas of the Ovary, Boston M. & S. J. **187**:1-13 (July 6) 1922. (*g'*) Sampson, J. A.: Intestinal Adenomas of Endometrial Type: Their Importance and Their Relation to Ovarian Hematomas of Endometrial Type (Perforating Hemorrhagic Cysts of the Ovary), Arch. Surg. **5**:217-280 (Sept.) 1922. (*h'*) Dougal, D.: Adenomyoma involving the Vermiform Appendix, J. Obst. & Gynaec. Brit. Emp. **30**:244-225 (Summer) 1923. (*i'*) Suzuki, S.: Über endometrioides Adenomyom und endometrioide Adenomatose des Wurmfortsatzes, Arch. path. Anat. **250**:579-594, 1924. (*j'*) Sampson, J. A.: Inguinal Endometriosis: Often Reported as Endometrial Tissue in the Groin, Adenomyoma in the Groin, and Adenomyoma of the Round Ligament, Am. J. Obst. & Gynec. **10**:462-503 (Oct.) 1925. (*k'*) Outerbridge, G. W.: Cystic Lesions of Possible Endometrial Origin in Appendix: Report of 4 Cases, ibid. **10**:545-552 (Oct.) 1925. (*l'*) Sampson, J. A.: Endometrial Carcinoma of the Ovary Arising in Endometrial Tissue in That Organ, Arch. Surg. **10**:1-72 (Jan.) 1925. (*m'*) Seelig, M. G.: Endometrial Adenoma (Implantation) in the Vermiform Appendix, Tr. Am. S. A. **43**:700-711, 1925. (*n'*) Dietlein, M.: Die Bedeutung der heterotopen Epithelwucherungen vom Bau der Uterusschleimhaut für die Chirurgie, Zentralbl. Chir. **54**:1346-1353 (May 28) 1927. (*o'*) Schochet, S.: Primary Adenocarcinoma of the Appendix, Am. J. Obst. & Gynec. **14**:684 (Nov.) 1927. (*p'*) Hosoi, K., and Meeker, L. H.: Endometriosis, Arch. Surg. **18**:63-99 (Jan.) 1929. (*q'*) Starr, F. N. G.: Endometrioma of Terminal Ileum, Appendix and Cecum, ibid. **19**:152-153 (July) 1929. (*r'*) Breuer, C.: Über das gleichzeitige Vorkommen von Tubenadenomyom: Teerzyste des Ovariums und Endometriosis des Wurmfortsatzes, Monatsschr. Geburtsh. u. Gynäk. **85**:30-42 (May) 1930. (*s'*) Milone, S.: L'endometrioma dell'appendice, Arch. per le

(Footnote continued on next page)

smelling, dark-purplish liquid. Roentgenography with barium sulfate enemas, using the double air-contrast method, was done on Aug. 31, Oct. 23, and Oct. 26, with consistently normal results. Proctosigmoidoscopy on Oct. 21 showed no abnormality. Finally, because the rectal bleeding continued unabated and a dangerously severe secondary anemia (red blood cell count, 1,640,000, and hemoglobin concentration, 38%) was developing, an abdominal pelvic exploration was performed at the Hollywood-Presbyterian Hospital on Nov. 13. A marked fourth-degree uterine retroversion was corrected by a suitable uterine suspension. Only a few scattered, small pelvic endometrial implants were found in the cul-de-sac. The rectosigmoid was grossly free from endometrial lesions. The vermiform appendix was clubbed at its tip, and its walls were greatly thickened. No other gross abnormalities were found after careful abdominal exploration. An appendectomy was done, and the stump was not inverted.

Summary of Data from the Literature

1. Incidence	0.377%*
2. Total number of cases reported	134†
3. Marital status:	
A. Single	17
B. Married (11 had 21 children; 2 had 1 abortion each)	41
C. Not stated	76
4. Average age (in 116 reported instances)	34.85 yr.
5. Location of endometrial lesions in vermiform appendix:	
A. At tip	19
B. In middle third	8
C. At base	2
D. On mesoappendical border	2
E. Location not stated	31
F. No data given	72
6. Associated pathologic findings:	
A. Marked endometriosis of right pelvic adnexa	29
(1) Tip of appendix adherent to right pelvic adnexa	7
(2) Definite tumor formation at tip of appendix	13
(3) Definite tumor formation at base of appendix	1
B. Right pelvic adnexa apparently normal	33
C. No data given	72
7. Cases reported here for the first time	9‡

* Between 1924 and 1951, 29 authors (including the present author) reported that endometriosis of the vermiform appendix was found in 92 instances among 26,496 examples of external endometriosis (Footnote 11*b* to *c'*).

† Between 1905 and 1951, 47 contributions (including the present study) were made: Sampson.[3] Footnote 11*c*, *d*, *f*, *j* to *l*, *n* to *t*, *v* to *z*, and *c'* to *c''*.

‡ These nine cases occurred in 4,080 consecutive appendectomies performed from June 29, 1947, to March 1, 1951, at the Hollywood-Presbyterian Hospital. The hospital case numbers were as follows: B-99249, C-4596, C-8329, C-8366, C-12083, C-35636, C-37555, C-45340, and C-47374.

sc. med. **54**:449-472 (July) 1930. (*t'*) Ewald, F. K.: Endometriosis des Wurmfortsatzes, Ztschr. Geburtsh. u. Gynäk. **108**:376-381, 1934. (*u'*) Cabot Case 21091, New England J. Med. **212**:394-397 (Feb. 28) 1935. (*v'*) Sutton, L. A.: Endometriosis, in Davis, C. H.: Gynecology and Obstetrics, Hagerstown, Md., W. F. Prior Company, Inc., 1935, Vol. 2, Ch. 16, pp. 1-113. (*w'*) Kulikowska, L.: Endométriose ovarienne et appendiculaire avec myxome de l'appendice, Gynéc. et obst. **36**:48-52 (July 1937. (*x'*) Votta, E. A.: Endometrioma de la región apendicular, Rev. cir. Buenos Aires **16**:480-493 (Oct.) 1937. (*y'*) Seelig, M. G., and Hobbs, J. E.: Endometriosis of the Vermiform Appendix, in Geist, S. H., and others: Anniversary Volume for Robert Tilden Frank, St. Louis, C. V. Mosby Company, 1937, pp. 209-225. (*z'*) Gauthier-Villars, P., and Lamy, M.: L'endométriome de l'appendice, Presse méd. **47**:423-426 (March 18) 1939. (*a''*) Jacobi, H.: Endometriosis externa bei Gynatresien, Zentralbl. Gynäk. **64**:867-877 (May 25) 1940. (*b''*) Plate, W. P., and Rottinghuis, H.: Endometriose der appendix en ontwikkelingsstoornis van het geslachtsorgaan, Nederl. tijdschr. geneesk. **85**:979-982 (March 8) 1941. (*c''*) Milnor, G. C., and Tilden, I. L.: Endometrial Cyst of the Groin Associated with a Decidual Reaction in the Appendix, Am. J. Obst. & Gynec. **44**:324-330 (Aug.) 1942.

The report (No. 13K-50-14) of the hospital pathologist (Dr. V. L. Andrews) was as follows:

The appendix measured 5.0 by 1.5 cm. The wall was pale, and the lumen contained a sanguineous exudate. Microscopic section through the appendix showed the wall and submucosa greatly thickened and fibrous. A diminished amount of lymphoid tissue, some edema, and round-cell infiltration in the lumen were noted. There were also present quite typical uterine glands in the serosa involving the musculature of the appendix, indicating that the patient had endometriosis of the appendix.

Photomicrograph (× 48). Note that extensive endometrial implant in subserosa is invading muscularis. There is an increase in fibrosis in this area. Patient had endometriosis of appendix with severe melena.

The photomicrograph depicts the histologic changes present.

The patient made an uneventful convalescence, leaving the hospital on the ninth postoperative day, her incision having healed per primam intentionem. She returned to her former occupation on Jan. 2, 1951, and has worked steadily ever since (nine months). There has been no further melena postoperatively. The hemogram is now entirely normal.

COMMENT

This is apparently the first recorded instance in which endometriosis of the vermiform appendix caused severe melena and a consequent marked secondary anemia within three months following the onset of symptoms.

CONCLUSIONS

The available literature on endometriosis of the vermiform appendix is reviewed and summarized.

A report is presented of a proved instance of endometriosis of the vermiform appendix that produced severe melena. The patient has remained well after an appendectomy. This apparently is the first recorded instance of severe melena resulting from appendical endometriosis.

Eight other proved instances of this appendical lesion are reported for the first time.

This study raises the total reported instances in the literature on endometriosis of the vermiform appendix to 134.

ADDENDUM

The following case report was contributed by Dr. Emmet A. Pearson, of Los Angeles from his personal case file. This report was received too late for inclusion in the above study.

Miss V. G., aged 23 years, had had no previous pregnancies. Three years prior to surgical treatment she had had an acute pelvic inflammatory disease, with cervical smears positive for a Neisserian infection. Pelvic laparotomy was performed on April 26, 1940. The uterus, tubes, ovaries, gall bladder, and duodenum were normal. The appendix was 3.5 by 1.3 cm., with a clubbed and lobulated tip buried in adhesive bands. An appendectomy was done. There was partial obliteration of the lumen at the tip. Microscopic examination of the appendix revealed diffuse chronic inflammation, with considerable hypertrophy of the muscularis at the tip. In the tip were seen glands of the endometrial type, some of which were surrounded by thin zones of cytogenic stroma containing a few deposits of old blood pigment. The diagnosis was endometriosis of the appendix.

LIGATION OF THE HEPATIC AND SPLENIC ARTERIES IN A PATIENT WITH ATROPHIC CIRRHOSIS OF THE LIVER

JACOB K. BERMAN, M.D.
LULLUS P. MULLER, M.D.
CHARLES FISCH, M.D.
AND
WILLIAM MARTZ, M.D.
INDIANAPOLIS

IN PREVIOUS experimental work one of us (J. K. B.) showed that ligation of the hepatic and splenic arteries was a rational procedure in the treatment of portal hypertension due to cirrhosis of the liver.[1] In another communication the experimental evidence which indicates that this maneuver is useful in man will be summarized.[2] After three years of investigation the senior author decided to try the operation on a patient with advanced cirrhosis of the liver. This man had ascites and bleeding varices. The following is a brief résumé of his case history together with laboratory findings:

E. C. H. is a white man 60 years of age who came to the Indianapolis General Hospital on Feb. 27, 1949, complaining of swelling of his feet and legs and dyspnea on exertion. For a period of 18 months prior to his admission he had been failing in health. He stated that he had lost his appetite and that there had been a gradual enlargement of his abdomen. In spite of this swelling he stated that he had lost 60 lb. (27 kg.) in weight. However, he continued to consume 6 to 10 bottles of beer and 1 to 2 pt. of whisky daily. This had been his habit for the past 30 years.

At the time of admission he was emaciated. There was pitting edema of the anterior abdominal wall, thighs, legs and feet, dulness of the lower half of the right chest and a greatly distended abdomen which was obviously filled with ascitic fluid. There was also a large umbilical hernia measuring approximately 4 by 6 in. (10 by 15 cm.) in diameter. Funduscopic examination showed grade II sclerosis, normal disks and no hemorrhages or exudates. The point of maximum impulse was at the level of the sixth rib in the midclavicular line. A soft systolic murmur was heard in the pulmonic and mitral areas. The cardiac rate was 72, with a normal rhythm, and the blood pressure was 100 systolic and 60 diastolic. Laboratory studies at this time showed the following values: globulin, 6.1 gm.; serum albumin, 2.1 gm., and sulfobromophthalein retention, 40% in 30 minutes and 31% in 45 minutes. During hospitalization it was necessary to do several abdominal paracenteses and also several thoracenteses for the relief of ascites and of the right hydrothorax. Other therapy included a low salt, low fat, high protein, high carbo-

Supported by a grant from the Charles J. Wolf Foundation for Medical Research.

From the departments of surgery and gastroenterology, Indianapolis General Hospital, and the Department of Surgery, Indiana University School of Medicine.

1. Berman, J. K.; Koenig, H., and Saint, W. K.: Ligation of the Hepatic and Splenic Arteries in the Treatment of Portal Hypertension, Quart. Bull. Indiana Univ. M. Center **12**(no. 4):99, 1950.

2. Berman, J. K., in discussion before Western Surgical Association, Minneapolis, Nov. 30, 1950.

hydrate diet, dried yeast U. S. P. (brewer's yeast) and protein mineral mix. The patient was also given mercurial diuretics, and he was discharged from the hospital on July 9, 1949, and followed in the gastrointestinal clinic as an outpatient.

On July 25, 1949, the patient weighed 228 lb. (103.5 kg.). This represented a 24 lb. (11 kg.) gain since his discharge from the hospital 16 days previously. The sulfobromophthalein retention at this time was 33% in 30 minutes and 23.8% in 45 minutes. The tota! protein content was 7.6 gm., with albumin 2.4 gm. and globulin 5.2 gm. On September 21, testosterone propionate was added to the treatment, and he was given 50 mg. twice a week.

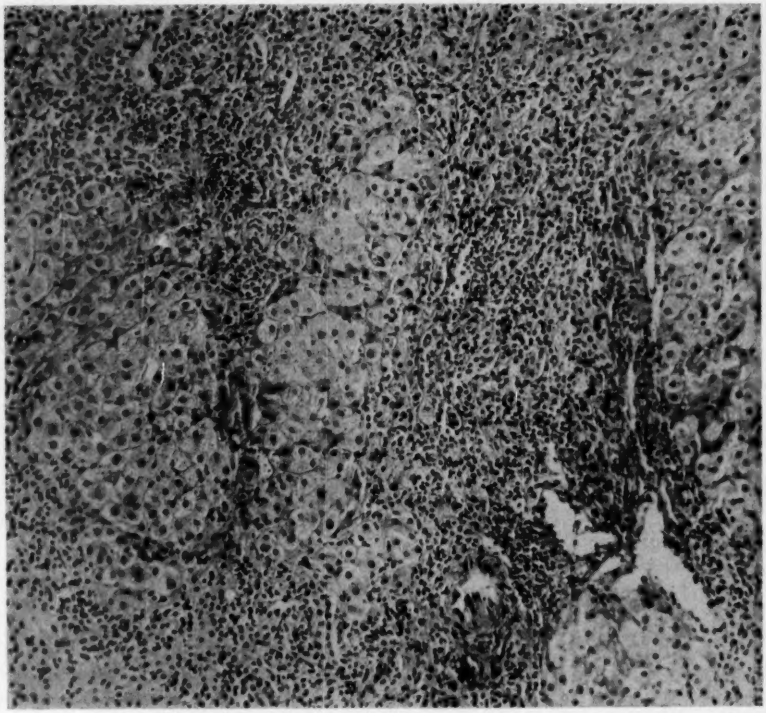

Fig. 1.—Biopsy specimen taken at time of operation shows active cirrhosis with dense periportal exudate containing occasional polymorphonuclear leucocytes. Liver lobules have been dissected by "invading" fibrous tissue with exudate, creating the typical picture of multilobular cirrhosis.

During the original admission numerous paracenteses were done, with an average removal of 17,855 cc. of fluid per month.

Throughout the period Dec. 4, 1949, to April 30, 1950, he was treated with a carboxylic type of cation exchange resin in doses ranging from 40 to 90 gm. per day. With this therapy his weight was maintained relatively constant. During this time he required one paracentesis.

Because of anorexia, weakness, and bloody diarrhea the patient returned to the hospital on April 30, 1950. At that time the resin therapy was discontinued. Consultants pointed out that persistent bloody diarrhea associated with a small liver was a grave prognostic sign in cirrhosis and that this patient was probably in a terminal phase of his disease.

During the next six months therapy consisted of a low salt diet and daily injections of mercurial diuretics. In spite of this treatment the patient required monthly paracenteses, with an average of 14,000 cc. of fluid being removed. His general condition remained about the same, and he was transferred to the Surgical Service on Nov. 16, 1950.

He was given crystalline procaine penicillin G in oil (duracillin in oil®), 1 cc., and streptomycin, 0.5 gm., twice a day intramuscularly. He was also given 500 cc. of whole blood on Nov. 20 and again on Nov. 21 at the time of operation.

On Nov. 21, 1950, the abdomen was opened through a left paramedian incision and approximately 7,500 cc. of a straw-colored fluid was aspirated from the abdominal cavity. The liver was extremely small and hard and was covered with a fibrinous exudate which seemed to be approximately 4 to 6 mm. thick. This same type of fibrinous deposit was present over all intra-abdominal organs. An incision was made in the gastrocolic omentum, and the portal vein was identified. An attempt to measure the portal pressure was discontinued because in cleaning off the portal vein a small plexus of adventitious veins was torn and a prodigious amount of bleeding was produced. Attempts to ligate these small thin-walled veins were unsuccessful, and therefore it was thought that if the previous experimental work was reliable ligation of the

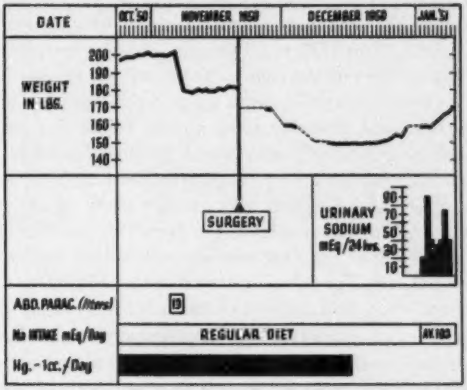

Fig. 2.—Data relative to the period of hospitalization from Oct. 24, 1949, to Jan. 9, 1951. Note the gradual loss of weight after operation, the increase of urinary sodium and later the relatively slow increase in weight while the patient was on unrestricted sodium intake.

hepatic artery would so reduce the portal pressure that the bleeding should stop spontaneously. Rather than consume more time controlling this bleeding in an attempt to get an accurate portal pressure, the hepatic artery was doubly ligated and the attempts to ligate the small adventitious veins were temporarily abandoned. The splenic artery was also ligated at the same time. Both vessels were tied close to the celiac axis with 0 silk ligatures. There was no change in systolic or diastolic blood pressure at the time of ligation or later throughout the procedure. A small biopsy was taken from the liver, and the defect was closed with three sutures of silk (Fig. 1). Inspection of the area that was bleeding prior to the ligation of the hepatic and splenic arteries showed no further hemorrhage, and therefore it was unnecessary to tie off the vessels mentioned. The abdomen was closed without drainage.

After operation administration of duracillin and streptomycin was continued until December 1. There was no postoperative fever. The patient was given a low fat, high carbohydrate, high protein diet without salt restriction, which he tolerated well. Within a few days after surgical intervention it became necessary to supplement the ordinary hospital diet because of an increase in the patient's appetite. He has been up and about the ward since Nov. 24, and there has been no ankle edema, no ascites and no dyspnea until Jan. 5, when a small amount of

ascites appeared which did not require tapping. He was put on a restricted salt diet of 3 gm. per day. Since this time there has been no further gain in weight and the ascites has receded (Fig. 2). The abdominal collateral veins which were present prior to operation are less pronounced. The esophageal varicosities are not now demonstrable on roentgenograms. During the previous periods in hospital and prior to operation the patient demanded an increasing amount of narcotic for the relief of a "bearing-down" abdominal pain. Prior to operation he was receiving methadon hydrochloride (dolophin®), 10 mg., or meperidine hydrochloride (demerol hydrochloride®), 100 mg., every few hours. Since December 14 he has received no narcotics, sedatives or analgesics.

COMMENT

The rationale for the ligation of the hepatic and splenic arteries in the treatment of cirrhosis of the liver will be described elsewhere.[3] Ligation and division of the hepatic artery is entirely feasible because of the rich anastomoses which occur when the artery is tied close to its origin. Circulation is ample and occurs through the left gastric artery, which anastomoses with the right gastric artery into the hepatic artery, and also through the accessory hepatic artery, which is present, according to Brunschwig,[4] in approximately 40% of cadavers. Another method of collateral circulation is by way of the superior mesenteric artery which gives rise to the right hepatic artery in about 12 to 15% of all persons. Lastly, branches develop through the inferior phrenic arteries or through an accessory left hepatic artery which may arise from the left gastric artery. No doubt many capricious anastomoses result from hepatic artery ligation and probably some appear before ligation in the cirrhotic liver. The circulation is probably maintained in most instances through the left gastric artery anastomosing with the right gastric artery and into the hepatic artery. However, in the experimental animal it is possible to tie off the celiac axis or the hepatic, left gastric and splenic arteries at the same time without in any way interfering with the circulation of the liver provided the animal has been prepared with penicillin and streptomycin. The splenic artery may be tied close to its source without producing necrosis of the spleen because of the rich blood supply through the short gastric and the gastroepiploic artery. Thus anatomically it is perfectly safe to tie off these large vessels close to their source. A fundamental axiom in the ligation of any large vessel is that the closer to its origin that an artery is tied the greater and more effective will be the collateral circulation.

Ligation of the hepatic artery in man is not new. Reports are present in the literature of ligation of the artery for the cure of aneurysm by Kehr,[5] Kading,[6] and Colmers.[7] In the case of Kehr the ligation was distal to the point of the gastroduodenal branch. In this case, no doubt, the circulation was maintained through the left gastric artery anastomosing with the right gastric artery and into the hepatic artery. Sudek is said to have ligated the artery proximal to all its branches with

3. Berman, J. K.: Ligation of the Hepatic and Splenic Arteries in the Treatment of Portal Hypertension: Experimental and Clinical Studies, to be published.

4. Brunschwig, A., and Clark, D. E.: Carcinoma of the Cystic Duct, Arch. Surg. **42**:1094 (June) 1941.

5. Kehr, H.: Der erste Fall von erfolgreicher Unterbindung der Arteria hepatica propria wegen Aneurysma, München. med. Wchnschr. **1**:1861, 1903.

6. Kading, K.: Ein geheilter Fall von intrahepatischen Aneurysma mit besonderer Berücksichtigung der traumatischen Leberarterie Aneurysmen, Deutsche Ztschr. Chir. **150**:82, 1919.

7. Colmers, F.: Intrahepatisches Aneurysma und Gallenfistel nach Leberzerreissung: Heilung durch Unterbindung der Arteria hepatica communes, Beitr. klin. Chir. **122**:324, 1921.

success. Colmers reported a cure of an intrahepatic aneurysm by ligation of the common hepatic artery.

The effects of hepatic and splenic artery ligation on the cirrhotic liver are, of course, unknown at present. We believe, however, that the possible effects may be described under three headings: (*a*) mechanical (*b*) functional, and (*c*) morphological. Under mechanical effects may be listed (1) a fall in portal pressure which results in the alleviation of varices and ascites and (2) an increase in the number of arteries supplying the liver because of collaterals. This procedure has produced no evidence of improvement in the function of the liver except for the sulfobromophthalein retention, which has returned to normal. (See Table for detailed data.)

*Liver Function Studies**

Date	Alkaline Phosphatase, Units	Total Protein, Gm.	Albumin, Gm.	Globulin, Gm.	Serum Bilirubin, Mg.	Sulfobromophthalein, % 30 Min.	Sulfobromophthalein, % 45 Min.	Cephalin-Cholesterol Flocculation 24 Hr.	Cephalin-Cholesterol Flocculation 48 Hr.	Thymol Turbidity	Colloidal Red	Prothrombin Time, %
3/17/49.....	25.2	6.9	2.3	4.6	0.55	19.2	15	3	3	2	..	..
4/ 8/49.....	28.5	6.3	2.3	4.0	0.41	19.7	15.4	1	3	3	..	..
6/16/49.....	20.4	6.3	3.1	3.2	.....	22.9	16	3	3	2	..	..
7/28/49.....	20.1	7.6	2.4	5.2	0.57	33.3	23.8	1	2	3	..	..
11/22/49.....	.....	5.4	2.2	3.2	.....	.....	..	..	..	..	..	..
12/ 6/49.....	.....	6.46	2.76	3.7	.....	20.0	14.9	1	3	Neg.	..	..
1/18/50.....	.....	7.2	3.25	3.95	.....	24	15	Neg.	3	..	..	..
2/22/50.....	.....	7.2	3.23	3.98	.....	36.5	15.9	1	4	2	..	..
3/24/50.....	19.0	7.8	3.7	4.1	0.4	.....	..	..	..	..	..	..
8/24/50.....	16.8	5.7	1.8	3.9	0.752	23	14	3	4	5	3	..
11/15/50.....	14.0	5.6	1.8	3.8	0.682	16.2	12	1	2	4	3	..
Operation, Nov. 21, 1950												
12/ 5/50.....	28.5	7.1	3.5	3.6	0.539	14.6	9.3	2	3	4	3	..
12/ 8/50.....	.....	...	...	...	.....	.....	..	..	..	..	..	62
12/12/50.....	21.2	7.5	3.6	3.9	0.402	25.8	17.6	3	..	7.5	3	..
12/16/50.....	.....	...	...	...	.....	.....	..	..	..	..	..	82
12/19/50.....	22.5	6.1	2.8	3.3	0.610	10.7	7.3	2	4	7.5	4	..
12/20/50.....	.....	...	...	...	.....	.....	..	..	..	..	..	70
12/26/50.....	21	6.7	2.7	4.0	0.610	.....	..	1	1	5	1	..

* The methods used were as follows: For alkaline phosphatase, modified King-Armstrong technique; serum proteins, modified Kjeldahl technique; serum bilirubin, Malloy and Evelyn technique; sulfobromophthalein 5 mg. of dye per kilogram of body weight; cephalin-cholesterol flocculation, Neefe and Rheinhold modification of Hanger's technique; thymol turbidity, Maclagan's technique; colloidal red, Ducci technique, and prothrombin time, Quick technique.

Before operation the patient excreted an average of 2 mEq. of sodium per 24 hours [8] (Fig. 2). Studies in process indicate that urinary excretion of sodium may have been increased by this procedure. The effect of the ligation of the hepatic and splenic arteries on systemic hypertension has not yet been evaluated by us. Clinically, cirrhosis and hypertension are seldom associated. However, there is as yet no explanation for this observation. The amount of renin subtrate (alpha-2-globulin) has been determined before and after surgical intervention in only one of our patients thus far and a significant increase in angiotonin units was found. Morphological studies made by needle biopsy showed no significant changes eight weeks after operation.

8. Layne, J. A., and Schemm, F. R.: The Use of a High Sodium Intake and a Low-Sodium Acid Ash Diet in the Management of Portal Cirrhosis with Ascites, Gastroenterology **9**:705, 1947. Eisenmenger, W. J.; Blondheim, S. H.; Bongiovanni, A. M., and Kunkel, H. G.: Electrolyte Studies on Patients with Cirrhosis of the Liver, J. Clin. Invest. **29**:1491, 1950.

SUMMARY

A man with advanced cirrhosis of the liver complicated by ascites and esophageal varices and bleeding from the gastrointestinal tract has been treated by the simultaneous ligation of the hepatic and splenic arteries. There has been only slight recurrence of ascites, which receded as soon as the patient was placed on a restricted salt diet, and none of the edema to date (six months). Preliminary data indicate increased urinary excretion of sodium. There has been no bleeding from the esophageal varices or other points in the gastrointestinal tract. The patient has shown a remarkable improvement in strength, appetite and general demeanor. Follow-up studies, including more biopsies of the liver, will be done at a later time and will be the subject of subsequent reports together with other cases in which this treatment is being used at the present time. Perhaps even better results may be obtained by dividing the arteries instead of simply ligating them so that recanalization cannot occur. This has been done successfully in five patients recently. Also the ingestion of unrestricted amounts of salt may be unwarranted in a patient with the extreme amount of liver destruction present in this case.

We are grateful to the Lilly Research Laboratories whose facilities were placed at our disposal during this study, and to William L. Drake, Jr., M.D., pathologist who personally supervised many of the laboratory tests.

DIVERTICULUM OF THE LEFT VENTRICLE OF THE HEART

Review of the Literature and Report of a Successful Removal of the Diverticulum

SAMUEL SKAPINKER, M.B., F.R.C.S.(Edin.)
JOHANNESBURG, SOUTH AFRICA

IN THE past few years, many strides have been made in the recognition, diagnosis and treatment of congenital lesions of the heart. This case of cardiac diverticulum is presented because of its rarity and to draw attention to the condition.

PREVIOUSLY REPORTED CASES

Twelve cases have been reported previously, and these are presented in the accompanying table.[1] In this series of 12 patients only one survived infancy without surgical intervention, and he died as a result of a rupture of his diverticulum at the age of 4 yr. Few of these cases were discovered at postmortem examinations, and in two the condition was recognized during life and surgical intervention undertaken. The first recorded attempt was that of Wieting (1912), who, on recognizing the condition, replaced the diverticulum into the pericardial sac without considering removal and closed the opening in the diaphragm. Roessler (1944) had a similar case which was recognized at birth, and he successfully resected the diverticulum. Unfortunately, no follow-up is available of Wieting's case, but Roessler's patient, when seen subsequently, had signs of other congenital lesions of the heart.

In an analysis of the cause of death in the 10 patients who died, it is found that two died of perforation of the diverticulum, one of congenital syphilis and bronchopneumonia, one of prematurity and one of multiple congenital defects. For the remaining five the cause of death is not given.

EMBRYOLOGY

The origin of a diverticulum of the left ventricle is difficult to explain on developmental lines, and the most satisfactory explanation is that of Drennan and van der Vijver (1928), who considered the diverticulum as a congenital defect. They postulated a developmental instability of the apex of the heart, which is not covered by our present knowledge of embryology.

From the Baragwanath Hospital and the Department of Surgery, University of Witwatersrand.

1. (*a*) Arnold, J.: Arch. path. Anat. **137**:318, 1894. (*b*) Ashoff: ibid. **144**:51, 1896. (*c*) Drennan, M. R., and Van der Vijver, G. T.: J. Med. A. South Africa **2**:58, 1928. (*d*) Gibert: Progr. méd. Paris **11**:446, 1883. (*e*) Iffert: Inaugural dissertion, 1938. (*f*) Koller-Aeby, H.: Arch. Gynaek. **82**:184, 1907. (*g*) Mahrburg, S.: Arch. path. Anat. **277**:498, 1930. (*h*) O'Bryan, in Peacock: On Malformations of the Human Heart, London, 1866. (*i*) Sweyer, A. J.; Mauss, I. H., and Rosenblatt, P.: Congenital Diverticulus of the Left Ventricle, Am. J. Dis. Child. **79**:111, 1950. (*j*) Von Thaden: Ztschr. f. rat. Med. **33**:58, 1865. (*k*) Wieting: Zentralbl. Chir. **114**:293, 1912.

Examination of the heart shows that although the apex is always drawn in illustrations as the thickest part of the heart wall it is in point of fact the thinnest. Drennan found that in 15 postmortem specimens of normal hearts the average thickness of the walls of the ventricle was 13 mm., as compared with the apex, which averaged only 2 mm. He also stated that the contour of the cavity of the left ventricle was such that there was a recess to within a few millimeters of the outer surface of the heart and suggested that this should be named the "apical recess."

Data on Reported Cases

Date	Author	Age and Sex of Patient	Anatomical Details	Result
1837	O'Bryan [1h]	3 mo.	Diverticulum of the left ventricle passing through the diaphragm into anterior abdominal wall	Died
1865	Von Thaden [1j]	5 mo., boy	5.3 cm. finger-like diverticulum of the left ventricle, passing into the anterior abdominal wall	Died
1883	Gibert [1d]	2 mo., girl	3.8 cm. finger-like diverticulum of the left ventricle, passing through the diaphragm, presenting in the epigastrium	Died
1894	Arnold [1a]	1½ mo., premature girl	1.1 cm. diverticulum from the apex, bent upward to the left like a hook	Died from congenital syphilis and bronchopneumonia
1896	Ashoff [1b]	?	Pathological specimen—diverticulum of both chambers, penetrating through diaphragm; 2.5 cm. protrusion formed hernia 3 cm. above umbilicus	.....
1907	Koller-Aeby [1f]	7 mo., premature girl	Diverticulum of left ventricle passing through diaphragm	Lived 3 hr.
1912	Wieting [1k]	3 yr., boy	Diverticulum of heart, no mention from which cavity, which passed through diaphragm; diverticulum replaced in pericardium and diaphragm closed	No follow-up available
1928	Drennan and Van der Vijver [1c]	6 yr., boy	Small pedunculated diverticulum of the left ventricle confined to the pericardium; ruptured	Died
1930	Mahrburg [1g]	3 days, boy	Diverticulum of the left ventricle, 5 cm. long, 1 cm. thick, passed through the diaphragm to present as a pulsating swelling of the cord	Died; had multiple congenital lesions, harelip, septal defect of the heart, acrania
1938	Iffert [1e]	Newborn girl	Diverticulum 4.5 cm. long, 3.5 cm. broad from both chambers, passing through a defect in the diaphragm; rupture of the umbilical cord on the 23rd day to sloughing of skin	Died
1944	Roessler	Newborn girl	Diverticulum of the left ventricle, 7 × 3 cm., passing through the diaphragm and presenting above the umbilicus; no sac	Successful ligation; had other congenital lesions of heart
1950	Sweyer, Mauss and Rosenblatt [1i]	3 hr., boy	Bifurcating diverticulum with bulbous termination 0.9 cm. in diameter; perforation of one sac; did not pass through diaphragm; apex of the other sac was tissue-paper thin	Died from perforation; no other congenital abnormality, except a patent ductus arteriosus
1950	Skapinker	5 mo., girl	Diverticulum of the left ventricle, 3 × 1.25 cm., passing through defect in anterior portion of diaphragm into umbilicus; serous-lined sac communicating with pericardium	Successful ligation

If such a recess is present, any increase in the intracardiac pressure should lead to a "blow out" at the apex and a diverticulum would be formed.

The formation of the diverticulum must occur before the final development of the diaphragm, as in the majority of cases described the diverticulum passes through a parasternal hiatus. In the case being reported the hernial sac was lined with pericardium.

In the cases of Drennan and van der Vijver (1928) and those of Sweyer and others (1950), the diverticula were small and did not pass down sufficiently to prevent the normal formation of the diaphragm. It is therefore suggested that the

diverticulum usually occurs before the final formation of the diaphragm. In Arnold's case (1894), however, the formation of the diverticulum must have occurred after the fusion of the diaphragm, as it was displaced upward and to the left side of the heart.

Although diverticula have been described communicating with the right and left ventricles, the majority are associated with the left ventricle. They are usually associated with other congenital defects, especially other lesions of the heart.

TREATMENT

As the present case is only the second one in which an operative removal of the diverticulum has been attempted, it is difficult to state whether removal should be done or not. Unfortunately, no follow-up record is available of the case in which the diverticulum was simply replaced in the pericardial sac, with closure of the diaphragm. However, we know from the recorded cases that the majority of

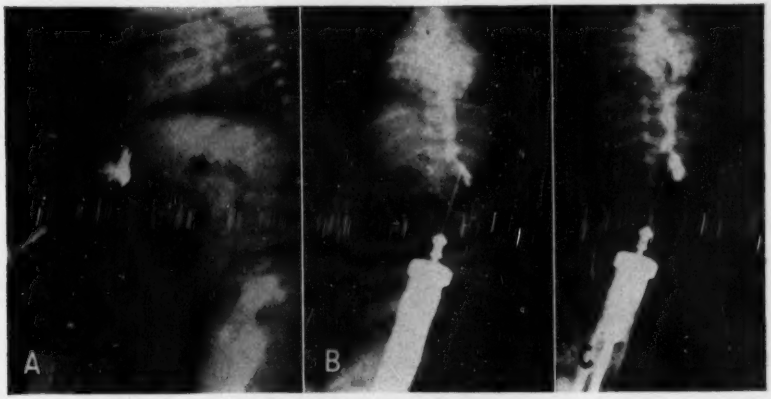

Fig. 1.—Angiograms showing (*A*) dye passing over diaphragm into left ventricle (lateral view) and (*B*) and (*C*) dye passing up into left ventricle (anteroposterior view).

patients die in the first few months of life and that in two cases sudden death occurred because of the rupture of the diverticulum. In the case of Iffert (1938), the diverticulum caused the skin of the umbilicus to slough and death occurred from secondary hemorrhage. On the basis of these facts, it is felt that operative removal should be attempted.

REPORT OF A CASE

The patient, a female Bantu child aged 2 mo., was brought by its mother to the Childrens Outpatient Department because of a rash on its face.

The rash was probably a contact dermatitis as it was customary to anoint the face with some oily preparation. On routine examination, it was noticed that the baby had a pulsating expansile tumor at the umbilicus, which according to the mother had been present since birth. The umbilical cord had presented no abnormality and had sloughed off in the usual manner on the sixth day. The baby was otherwise normal and healthy.

On further examination, the pulsating tumor was seen and felt at the umbilicus. It was expansile and not attached to skin. The pulse waves could be seen passing upward. The tumor

commenced at the umbilicus and passed up slightly to the left of the midline to under the costal margin. A "to-and-fro" murmur could be heard over it and a systolic murmur over the precordium.

On Aug. 10, 1950, an angiogram was performed with the patient in the lateral position (Fig. 1*A*). Twenty cubic centimeters of 50% perabrodil (iodopyracet injection) was given, and a series of roentgenograms was taken. The roentgenogram shows the dye passing immediately upward, over the diaphragm and diffusing into the heart shadow.

After the injection the patient showed a mild iodine reaction and had a slight pyrexia, which subsided in 24 hr.

On August 22 the angiogram was repeated, with the patient supine. The dye (again 50% perabrodil) passed up on the left side and disappeared in the region of the left ventricle (Figs. 1*B* and *C*, the former showing the diverticulum in systole and the latter in diastole). This second injection was undertaken after exposure of the anterior surface of the mass, which lay in a serous cavity immediately below the skin. (Fig. 2 is a diagrammatic interpretation of the angiograms.)

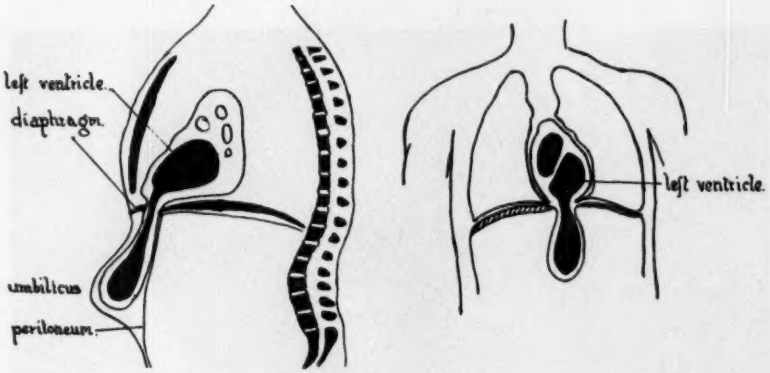

Fig. 2.—Schematic illustration of the condition: left, lateral view; right, anterior view.

Operation was performed on September 1, with the patient under open ether and oxygen anesthesia. A long right paramedian incision was made, and after the peritoneum was opened, a mass was felt lying immediately anterior to the peritoneum. The peritoneum was then dissected from the anterior abdominal wall and a smooth tumor isolated, which was pulsating. On upward dissection, it passed through a deficiency in the diaphragm, and further delivery showed that it communicated with the left ventricle. It contracted synchronously with the heart. The serous cavity that held the diverticulum was in direct communication with the pericardial sac.

Two artery forceps were placed across the base of the diverticulum, which was severed. No change or stoppage of the heart was noticed. Roessler stated that in his case when the base was first clamped the heart stopped beating and only after repeated attempts could he ligate it. After ligation of the pedicle, the myocardium was apposed with surgical gut sutures.

The pericardium was closed, but the hiatus in the diaphragm was not sutured.

Postoperatively, the child had persistent tachycardia and the systolic murmur which was previously present disappeared. A roentgenogram made on September 5 showed gross dilatation of the heart. The electrocardiograph revealed left axis deviation.

Later it was noticed that a swelling occurred in the incision and was due to a pericardial effusion causing the pericardium to herniate through the gap in the diaphragm. This swelling subsequently subsided.

The specimen (Fig. 3) when removed was found to be smooth-walled and measured 3 cm. long and 1.25 cm. wide. It was gray. On section it showed a thick-walled cavity that had a diameter of 3.5 mm., with walls the same thickness. Papillary muscles and chordae tendineae ran from the apex to the base of the cavity.

Microscopic section of the wall of the diverticulum showed normal cardiac muscle.

COMMENT

The diagnosis of a diverticulum of the heart should be borne in mind in every case in which a pulsating swelling occurs in the region of the umbilicus. Angiograms should be a great aid in the diagnosis, and it is believed that those presented here are the first ever produced of a diverticulum of the heart.

Fig. 3.—Diverticulum of the left ventricle after removal, twice normal size.

It is felt that the ligation and cardiac irritation such as observed by Roessler could be overcome by filling the pericardiac sac with procaine hydrochloride. It is interesting to note that firm pressure on the base of the diverticulum was not sufficient to stop the intrinsic contraction of the heart muscle of the diverticulum.

The marked tachycardia that occurred after the operation and continued for several days is thought to have been due to the extra strain placed on the heart because a cavity approximately one-third of the ventricles of the heart had been removed. This strain also caused the compensatory dilatation of the heart. Roessler described a similar experience. In this case the cardiac enlargement subsided in the third week, but in Roessler's case no amelioration of the size of the heart occurred, probably because of the other cardiac abnormalities, which were only recognized later.

When the patient was seen eight weeks later the heart had become nearly normal in size and there was no arrhythmia or abnormal heart sounds. There is still a defect in the diaphragm which can be observed when the baby strains or cries and through which the pulsations of the heart can easily be felt. It is proposed at a later date to close this hole, as it is a potential site for a hernia. The baby is otherwise healthy and is gaining weight.

SUMMARY

A review of 13 cases of diverticulum of the heart is presented. The suggested embryology of the condition is discussed, and late results and treatment are described.

INTERNAL BILIARY FISTULA DUE TO PEPTIC ULCER

JAMES M. SULLIVAN, M.D.
AND
LOUIS HAMMAN, M.D.
MILWAUKEE

SPONTANEOUS internal biliary fistula is not an uncommon complication of neglected cholelithiasis, peptic ulcers, and carcinoma. The incidence, as given by various authors,[1] differs but seems to vary between 3 and 5% of all cases of biliary disease. During the past three years there have been 60 patients with disorders of the biliary tract at this hospital who either have been operated on or have come to autopsy. Of these, there have been two with internal biliary fistula, due to peptic ulcer in both.

ETIOLOGY

Hicken and Coray [1b] state that 90% of biliary fistulas are caused by cholelithiasis and 6% are due to perforation of a peptic ulcer eroding into another viscus. The remaining 4% are due to carcinoma.

An internal biliary fistula, once established, generally remains open until the cause has been removed. Not only may the original fistula remain, but additional fistulas between other organs occasionally develop. The formation of a fistula usually intensifies the symptoms of a patient with gallbladder disease, and a patient with a peptic ulcer in whom a biliary fistula develops usually has symptoms of gallbladder disease added to the gastric complaints.[2] Occasionally, however, the acute symptoms of cholecystitis are immediately and dramatically relieved by the development of a fistula.[3]

The diagnosis can be confirmed roentgenologically if air can be demonstrated in the biliary system or if barium sulfate gets into it in a gastrointestinal series,[4]

From the Department of Surgery, Veterans Administration Hospital, Wood, Wis. and the Marquette University School of Medicine.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. (*a*) Judd, E. S., and Burden, V. G.: Internal Bilary Fistula, Ann. Surg. **81**:305-312 (Jan.) 1925. (*b*) Hicken, N. F., and Coray, Q. B.: Spontaneous Gastro-Intestinal Biliary Fistulas, Surg., Gynec. & Obst. **82**:723-730 (June) 1946. (*c*) Puestow, C. B.: Spontaneous Internal Biliary Fistula, Ann. Surg. **115**:1043-1054 (June) 1942. (*d*) Davison, M., and Aries, L. J.: Spontaneous Choledochogastrostomy and Cholecystogastrostomy, Ann. Surg. **107**:229-237 (Feb.) 1938.

2. Noskin, E. A.; Strauss, A. A., and Strauss, S. F.: Spontaneous Internal Biliary Fistula, Ann. Surg. **130**:270-276 (Aug.) 1949.

3. Dean, G. O.: Internal Biliary Fistulas, Surgery **5**:857-864 (June) 1939.

4. Garland, L. H., and Brown, J. M.: Roentgen Diagnosis of Spontaneous Internal Biliary Fistulae, Especially Those Involving the Common Duct, Radiology **39**:154-159 (Feb.) 1942.

although some dissenting opinions exist.[5] An atonic sphincter of Oddi is so rare that it need not be considered as permitting air or barium sulfate to get into the biliary system.[6] Emphysematous cholecystitis is also extremely rare, and when a diagnosis of this disease is made we feel that it is pathognomonic of internal biliary fistula.

The first, and most important, phase of treatment should be prophylactic. This involves cholecystectomy whenever gallstones are found, unless there is some contraindication. Peptic ulcers that do not respond to medical management should be operated on. In the case of carcinoma, early recognition and removal are important. The active treatment consists in the removal of the fistulous tract, if

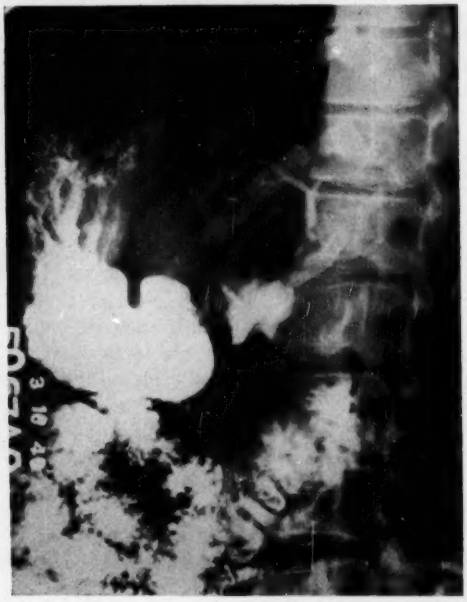

Fig. 1 (Case 1).—Roentgenogram shows barium sulfate in the biliary system and clearly demonstrates a choledochoduodenal fistula.

possible, and decompression of the biliary tract by elimination of common duct obstruction. Cholecystectomy should also be carried out when stones are found. In the case of an ulcer, gastric resection and obliteration of the fistulous tract, when feasible, is the treatment of choice.

CASE 1.—A 27-yr.-old white man came to the hospital with the chief complaint of pain in the right upper quadrant which radiated to the back for the past four months. The present illness apparently started at least 10 yr. before, at which time the patient first had epigastric

5. Eliason, E. L., and Stevens, L. W.: Spontaneous Internal Biliary Fistula, Am. J. Surg. **51**:387-392 (Feb.) 1941. Judd and Burden.[3a]

6. Rees, C. E.: Duodenocolic Fistula with Incompetent Sphincter of Oddi, J. A. M. A. **100**:496-497 (Feb. 18) 1933.

pains which were relieved by food and alkali and became asymptomatic. In 1948 the symptoms recurred and were at this time associated with nausea and vomiting. It was felt that the symptoms were out of proportion to the lesion, and a diagnosis of psychogenic gastrointestinal reaction was made. In February and May of 1949 the patient had two small slight hematemeses which were associated with tarry stools. After this another roentgenogram was taken, which clearly demonstrated a choledochoduodenal fistula (Fig. 1). The patient was discharged on a medical regimen but was again admitted in December, with the added complaints of pain in the right upper quadrant. He no longer got relief by taking food or alkalis, and the pain was aggravated by the intake of many different foods, particularly fried or fatty foods.

Physical examination showed only slight tenderness in the midepigastrium. There was no muscle spasm or rigidity. No rebound tenderness was noted.

Laboratory Data.—Routine blood and urine studies gave normal results. The roentgenograms again demonstrated the choledochoduodenal fistula.

Course in the Hospital.—It was decided that the patient had a duodenal ulcer which had perforated into the common duct, and he was therefore operated on. Many adhesions were found between the gallbladder and the duodenum. After the adhesions were divided the gallbladder was found to be thin-walled, emptied easily and contained no palpable stones. In the second portion of the duodenum, about 4 cm. distal to the pyloric ring, there was a scarred area which was indurated and densely adherent to the surrounding structures, particularly to the hepatico-

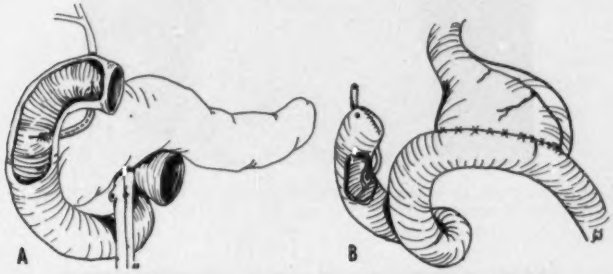

Fig. 2 (Case 1).—*A*, findings at operation. The probe is inserted from the duodenum through the fistula and into the common duct. *B*, gastric resection, by-passing fistula without disturbing it.

duodenal ligament. The proximal portion of the common duct was exposed and was found to be within normal size; no stones were palpable. The stomach was opened, and a finger was inserted down through the pylorus into the duodenum. At about 3 cm. beyond the pylorus a dense band of adhesions was found, through which a finger could be inserted with difficulty. Just distal to this ring of adhesions, an ulcer crater could be felt on the posterior wall of the duodenum. The duodenum was opened, and in the center of the ulcer a small fistula was found which went into the common duct. A probe could be passed through this fistula up into the common duct beyond the cystic duct, and it could be passed down the common duct into the ampulla of Vater. A gastric resection was carried out, with an anterior Polya anastomosis. The duodenal stump was closed just proximal to the fistula. The fistula was left in place and was not closed.

The postoperative course was uneventful save for diarrhea, which subsided spontaneously. The postoperative laboratory data were normal, and the serum bilirubin was at no time increased. The patient was discharged on a bland diet and has remained entirely asymptomatic.

Case 2.—A 52-yr.-old white man came to this hospital with the chief complaint of "a malignant tumor of the digestive tract." The present illness started about three years previously with shooting pains in the arms and legs and a progressive weakness, which became steadily worse until the time of admission. About one year before admission anorexia developed, and he had lost 27 lb. (12 kg.) since that time. About three months before his admission nausea and vomiting developed, and the patient was told that he had a malignant tumor of the digestive tract.

Fig. 3.—Postoperative gastrointestinal roentgenogram in Case 1. The fistula has been by-passed, and there is no further reflex into the biliary system.

Fig. 4 (Case 2).—The gastrointestinal roentgenogram shows barium sulfate in the biliary system.

He also had his first hematemesis and then had four more, each of which was followed by tarry stools. Prior to this time he had had no specific abdominal pains; however, he soon noticed that whenever he ate solid foods he suffered from epigastric pains which radiated to his back. Also, for the three months prior to his admission he had been bothered by gas and eructations.

Physical examination revealed a pale, thin, white man who appeared chronically ill. The heart and lungs were not remarkable. The abdomen was tense and tympanitic and distended with gas. There was no tenderness. There were no masses or solid viscera felt. The remainder of the physical examination showed no abnormalities save for some bizzare neurological findings.

Laboratory Data.—Routine blood and urine examinations showed moderate anemia, with 8.5 gm. of hemoglobin per 100 cc. of blood, and a trace of albumin in the urine. Gastric analysis showed a high total acidity of 66 degrees and a high free acid level of 44 degrees. A series of gastrointestinal roentgenograms showed an obstructive lesion at the outlet of the stomach and a reflux of barium sulfate into the hepatic ducts.

Course in the Hospital.—The patient was advised to undergo an operation but refused. He was therefore given symptomatic care while attempts were made to improve his anemia and general condition (and to convince him of the need for surgical intervention). However, on

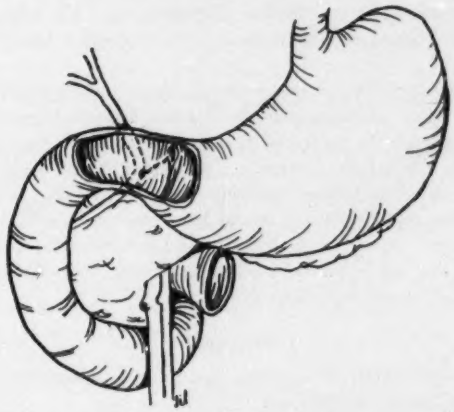

Fig. 5 (Case 2).—Autopsy findings. A probe is inserted from the stomach through the fistula and into the common duct.

the 14th hospital day he suffered what was thought to have been a thrombosis of a cerebral vessels, and the left side of his body became paralyzed. After this accident his course worsened progressively, and he died on his 27th day in the hospital.

Autopsy Findings.—The head was not examined. There was bilateral bronchopneumonia, which was probably the immediate cause of death. The examination of the abdominal viscera showed a firm mass of fibrous tissue in the region of the common duct. The duct was not dilated and emptied into the ampulla of Vater along with the pancreatic duct; it also emptied into an ulceration on the lesser curvature of the stomach through a fistulous tract over the surface of the pancreas. The gastric ulceration was located 1.5 cm. from the pyloric ring on the lesser curvature. The mucosa about the ulcerated area was indurated and thickened, and the fistulous opening was about 1 cm. in diameter. Microscopic sections showed no evidence of carcinoma.

ANALYSIS OF CASES

The first case illustrates one of the complications of duodenal ulcer and one of the dangers which might be encountered during gastric resection. Fortunately, the diagnosis was well established by roentgen examination before the operation

was undertaken. The common and hepatic ducts are well outlined by barium sulfate in Figure 1. It is our conviction that this sign is pathognomonic of an internal biliary fistula. The findings at operation (Fig. 2*A*) were what one would have expected after seeing the roentgenogram. Had it not been known that this fistula existed the common duct might well have been damaged during the removal of the ulcer or the fistula might have been transected and not closed. In either event, the outcome would have been disastrous. There are two points of interest in the history of this patient. The first is that a diagnosis of psychogenic gastrointestinal reaction was made and medical management was persisted in despite the findings of a choledochoduodenal fistula. The second point is that the symptoms of cholangitis, manifested by pain in the right upper quadrant, did not appear until several months after the fistula was demonstrated on roentgenograms. The treatment was gastric resection by-passing the fistula, which was not disturbed (Fig. 2*B*). In this case it was felt that the dissection necessary to remove the fistula would require unwarranted trauma to the common duct and would invite future stricture. Postoperative gastrointestinal roentgenograms show that the fistula has been adequately by-passed and that there is no further reflux into the biliary system (Fig. 3).

The second case also illustrates one of the dangers which might be encountered during gastric resection and is an example of a complication of gastric ulcer. Again the diagnosis was made by means of roentgenograms. In Figure 4 one can see barium sulfate in the biliary system. Unfortunately, the patient died from a cerebral vascular accident before treatment was undertaken. The autopsy findings (Fig. 5) show that this lesion would have lent itself well to operative cure. Gastric resection and excision of the fistula would have been the treatment of choice. Here again, were one not forewarned before operation, the same dangers of injury to the common duct would have been present.

CONCLUSIONS

1. Internal biliary fistula is a serious but not too uncommon complication of peptic ulcer as well as of cholelithiasis.

2. Formation of a spontaneous internal biliary fistula usually intensifies and complicates the symptoms.

3. Diagnosis can usually be made by x-ray visualization of air or of barium sulfate in the biliary system.

4. An internal biliary fistula may complicate gastric resection and if unrecognized may be disastrous.

EFFECT OF INTRAPERITONEALLY INJECTED BENZALKONIUM (ZEPHIRAN®) CHLORIDE

WILLIAM P. KLEITSCH, M.D.
AND
CHARLES F. HEIDER Jr., M.D.
OMAHA

THE USE of benzalkonium (zephiran®) chloride (alkylbenzyldimethylammonium chloride) as an antiseptic and germicide is based on confirmed laboratory and clinical evidence.[1] Its greatest field of usefulness has been as a skin disinfectant to prepare both the patient's skin for an incision and the surgeon's hands for an operation. It has been recommended for use in the vagina in preparation for an operation and in the bladder as an irrigating agent. We have used it extensively as a skin disinfectant as well as a means of preparing the mouth for oral surgery. In all these instances, if a 1:1,000 solution is used, reactions to the chemical are practically nonexistent.

We have further discovered that the detergent and germicidal properties of zephiran® make it desirable for use in hand basins during an operation. However, the concept of transferring the nonirritating and nontoxic properties of zephiran® on the skin to serosal surfaces did not seem justified, and since when used in hand basins some peritoneal implantation will result, it was felt wise to determine this effect of the disinfectant.

EXPERIMENTS

Five groups of experiments were made using white mice, guinea pigs and rabbits as subjects and 12.8% and 1:1,000 zephiran® chloride solutions as the agents tested. The 12.8% solution is a concentrate and ordinarily is not used clinically. The 1:1,000 solution is commonly used for skin preparation and is the one which we use in our hand basins. This dilution has been shown to have consistent germicidal properties. All solutions tested were injected intraperitoneally.

Dr. Heider is now on active duty with the Air Force.

This study was completed in the Veterans Administration Hospital, Lincoln, Neb.

From the Surgical Service of the Veterans Hospital and the Creighton University School of Medicine.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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Series I.—Series I consisted of six white mice weighing between 18 and 24 gm. Each was given an intraperitoneal injection of 0.25 cc. of concentrated 12.8% zephiran® chloride. All showed an immediate reaction to the injection characterized by a cessation of normal activity, a listless attitude, and death within 20 min. Gross examination of the viscera after death revealed no unusual findings. The microscopic findings were uniform. The lungs were congested and edematous. The cells of the heart muscle were swollen and showed clumping of the protoplasm. The kidneys exhibited generalized cloudy swelling and congestion. The liver usually was involved in cloudy swelling and frequently showed periportal infiltration with polymorphonuclear cells. The intestine showed only a serosal edema, and there was also marked edema in the parietal peritoneum. These findings were interpreted as

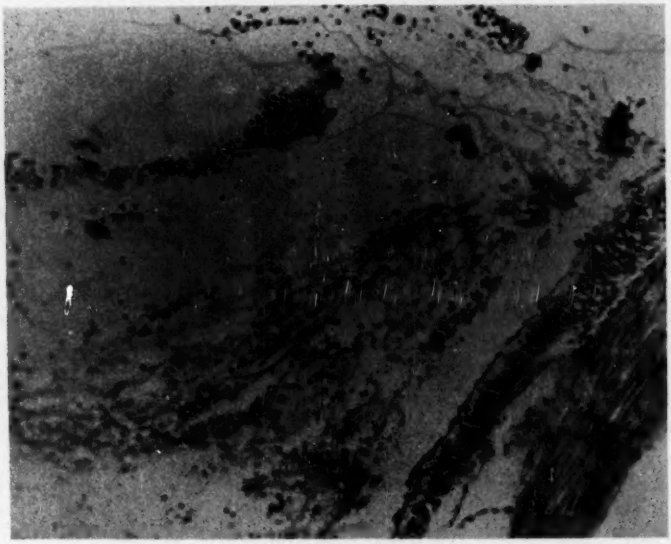

Fig. 1.—Photomicrograph of the visceral peritoneum typical of the reaction to 12.8% zephiran® chloride solution. Note the edema and leucocytic infiltrate between the serosa and the muscularis.

indicating that the dose used was toxic, and definite conclusions concerning the irritating effect of the solution on the serosa could not be drawn. The presence of edema, however, suggested that this concentration of zephiran® solution is not without some immediately irritating effect on serosal surfaces.

Series II.—Series II consisted of six guinea pigs weighing between 455 and 715 gm. which were given an injection of 0.5 cc. of concentrated 12.8% zephiran® chloride solution intraperitoneally. None of the animals showed any immediate response to the injection. Two, however, died within 24 hr. Gross examination revealed a bloody, serous fluid in their peritoneal cavities. One of these also showed adhesions at the site of injection. Microscopic examination revealed congestion and edema of the lungs and heart muscle. There was a cloudy swelling of the liver and kidneys.

The serosal surface of the intestine, as well as the parietal peritoneum, was edematous and congested with a slight exudate on its surface. These two guinea pigs were considered to have died a toxic death and to have shown a moderately severe peritoneal reaction to the injection.

The four remaining guinea pigs were disposed of as follows: One was killed at 72 hr., two at 96 hr., and one 16 days after injection. Gross examination revealed an area of localized peritonitis in the animal killed after 72 hr. and a 2 cm. intraperitoneal granuloma in the animal killed after 16 days. The other two animals

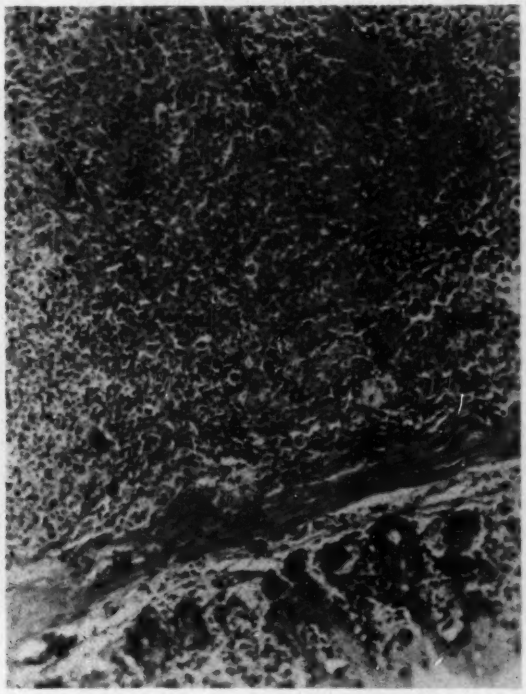

Fig. 2.—Photomicrograph of a granuloma produced by the intraperitoneal injection of 12.8% zephiran® chloride solution. Note that the entire thickness of the bowel wall is involved. Several giant cells can be identified.

had no gross change in the intraperitoneal organs. The microscopic findings were consistent. The lungs showed evidence of congestion and edema, one animal having frank bronchopneumonia. There was fatty degeneration in all the livers, varying from moderate to severe. This would suggest that the toxic process, seen in the acute deaths as a cloudy swelling, will progress with sublethal doses to a fatty degeneration of the liver cells. The serosal surface of the intestine and the peritoneum showed edema and congestion in all animals (Fig. 1). In the two with a gross peritoneal reaction, this process had gone on to focal necrosis with an acute

inflammatory response. Foreign body giant cells could also be demonstrated (Fig. 2). These four animals were considered to have shown evidence of a sublethal toxicity with moderate to severe peritoneal reaction to 12.8% zephiran® chloride solution.

Series III.—Series III consisted of six guinea pigs, weighing from 702 to 877 gm., which were given an intraperitoneal injection of 0.5 cc. of 1:1,000 zephiran® solution. All the animals survived and were killed at 24, 48, 72 and 76 hr. and after 5 and 14 days. Gross examination revealed no pathologic changes in any of the animals. Microscopic examination in general showed a normal picture. The animal killed after 48 hr. had congestion and hyperemia of the kidneys. The animals killed after 3, 4 and 5 days had evidence of dark, cloudy swelling of the liver and early,

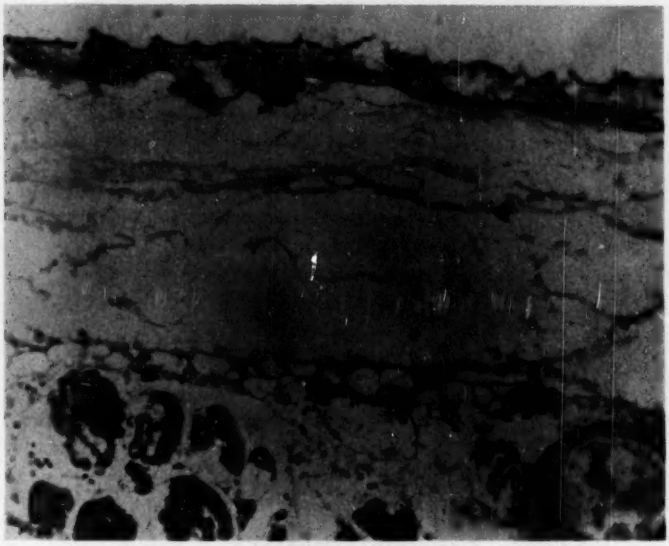

Fig. 3.—Serosal edema and leucocytic infiltration in the bowel of a rabbit following the intraperitoneal injection of zephiran® chloride 12.8%.

fatty metamorphosis. The serosa of the intestine and the peritoneum was normal in every animal. These findings were interpreted as showing some toxic changes in four of the animals and a peritoneal reaction in none of them.

Series IV.—Series IV consisted of six rabbits, weighing from 1,875 to 3,275 gm., which were given an intraperitoneal injection of 1 cc. of concentrated 12.8% zephiran® chloride solution. Three of the animals died within 24 hr., and one died after 48 hr. The remaining two rabbits were killed after 5 and 14 days. The three rabbits which died within 24 hr. showed similar pathologic changes. On gross examination, 10 to 15 cc. of rusty, serous fluid was found in the peritoneal cavity. The peritoneum was roughened, dull and covered with flecks of fibrin. Fibrinous adhesions matted the bowel together. On microscopic examination all three of these

animals showed evidence of pulmonary edema. There was evidence of cloudy swelling of the liver, and the kidneys were congested, especially in the capillary tufts. The peritoneum of the intestine as well as the parietal peritoneum was edematous and infiltrated with polymorphonuclear cells (Fig. 3). These cells extended out into the mesenteric fat and into the subperitoneal space. The surface of the peritoneum was covered with an amorphous exudate. The fourth rabbit, which died after 48 hr., showed essentially the same findings. In addition, there was evidence of bronchopneumonia and of degeneration of the proximal convoluted tubules of the kidney. Rabbit No. 5 and 6 were killed after 5 and 14 days, respectively. Gross examination of the organs showed nothing remarkable. Microscopic examination revealed bronchopneumonia in each. Both livers were abnormal, one

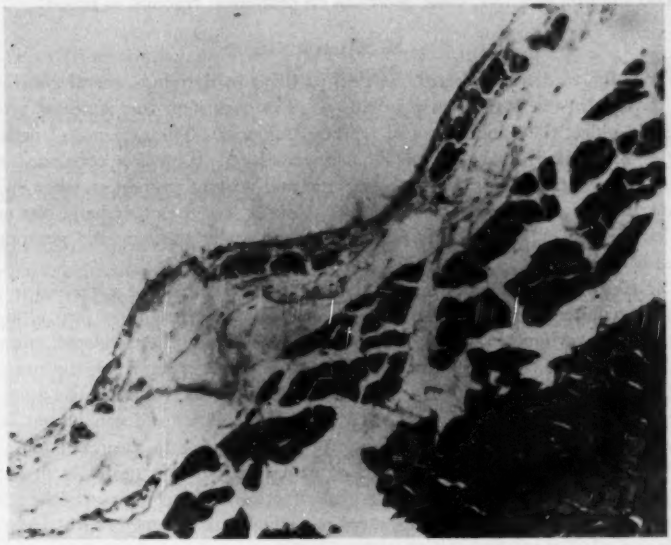

Fig. 4.—Photomicrograph of a section through a rabbit's bowel four days after the intraperitoneal injection of 1:1,000 zephiran® chloride solution. Note that the appearance of the tissues is essentially normal.

showing cloudy swelling and the other passive congestion. The peritoneum was not abnormal in either instance.

These results were interpreted as showing evidence of acute, fatal toxicity in three rabbits and a sublethal toxemia in the remaining three. A moderately severe peritoneal reaction was present in all but the last two rabbits.

Series V.—Series V consisted of six rabbits, weighing between 1,100 and 1,500 gm., which were given an injection of 1 cc. of 1:1,000 zephiran® chloride solution intraperitoneally. All but two of these animals died of pneumonitis, but the abdominal findings are nevertheless significant enough to report. Two of the rabbits died within 18 hr. and one 72 hr. after the injection. Gross examination revealed no abnormalities except for evidence of pneumonia. Microscopic examination like-

wise revealed nothing abnormal with the exception of pneumonia. The fourth animal was killed four days after injection. Both gross and microscopic examination revealed nothing abnormal in this animal (Fig. 4). The fifth rabbit died of pneumonia on the fifth day but had no other evidence of pathologic changes. The last rabbit was killed on the 14th day and had some intra-abdominal adhesions. Microscopic examination revealed patchy pneumonitis and fatty metamorphosis of the liver.

It was unfortunate that this final experiment was conducted at a time when an epidemic of pneumonitis afflicted our rabbit population. However, since this study was mainly directed toward the determination of peritoneal effects, it was felt to be worth while to include this group, since none of the rabbits showed evidence of peritoneal irritation. It was felt that one could conclude that zephiran® chloride, 1 : 1,000 solution in a 1 cc. dose, produces no peritoneal reaction in rabbits.

COMMENT

From the evidence collected, we feel justified in deriving several conclusions. The changes in the parenchymal organs were so consistent that it seems probable that they reflect the toxic effects of zephiran® chloride. The evidence of peritoneal reaction to the 12.8% solution was likewise consistent. It must be concluded, therefore, that zephiran® chloride has both toxic and irritant properties when injected intraperitoneally as a concentrated 12.8% solution. On the other hand, the recommended dilution of 1 : 1,000 was found to be practically nontoxic and nonirritating in the doses used.

We feel that on the basis of this evidence caution should be exercised in using 1 : 1,000 zephiran® chloride solution for irrigation or instillation into either the pleural or the peritoneal cavities. Unless all the solution can be recovered, one would run the risk of leaving a toxic amount behind. On the other hand, the use of the 1 : 1,000 solution in hand basins would appear to be perfectly safe. The amount of solution adhering to the gloves after washing is minimal and can be yet further reduced by wiping with a gauze sponge before returning to the operation.

We have found a 1 : 1,000 solution of zephiran® chloride desirable in surgical hand basins for its germicidal and detergent effects. Its presence assures the surgeon of a constantly sterile wash water and not one which will become progressively more contaminated as the operation proceeds. Its detergent properties make it peculiarly effective in removing dusting powder from the gloves prior to the operation and for cleaning off fat and blood during the operation. By effectively removing fat from the surgeon's gloves, it indirectly facilitates surgical procedures on obese persons. We have used zephiran® chloride 1 : 1,000 solution in surgical wash basins in over 2,000 operations. There has been no clinical evidence of irritation or of interference with healing.

SUMMARY

The effect of intraperitoneally injected zephiran® chloride solution was noted in white mice, guinea pigs and rabbits.

Ordinarily used dilutions (1 : 1,000) were nonirritant to peritoneal surfaces. Concentrated solutions (12.8%) were both toxic and irritant.

Zephiran® chloride 1 : 1,000 is a safe solution to use in surgical hand basins during an operation.

CORTISONE OR CORTICOTROPIN FOR ASTHMATIC PATIENTS WHO REQUIRE MAJOR SURGICAL PROCEDURES

LOUIS E. PRICKMAN, M.D.
GILES A. KOELSCHE, M.D.
HADDON M. CARRYER, M.D.
CHARLES K. MAYTUM, M.D.
AND
GUSTAVUS A. PETERS, M.D.
ROCHESTER, MINN.

IT IS NECESSARY to delay most major surgical procedures for patients who have asthma until the patient's cough, paroxysmal dyspnea and orthopnea are well controlled. This is particularly important in surgical procedures directed to the thoracic, renal and upper abdominal areas, in which splinting of the diaphragm commonly occurs postoperatively.[1] Usually, but not always, a preliminary period of hospitalization with symptomatic treatment and appropriate attention to any existing complications of asthma suffices to get the patient ready for the needed operation. However, we have recently encountered difficulty in bringing asthma under control within a reasonable period in four patients who needed surgical attention. In one patient who had colic from gallstones while she was receiving preoperative treatment of her asthma, cortisone brought about prompt remission of the asthma, which permitted successful and uncomplicated cholecystectomy. For a second patient who had a large incarcerated umbilical hernia, corticotropin (ACTH) was resorted to when other measures were not adequate to control her asthma and to make repair feasible. The third patient, who had intractable asthma and vasomotor rhinitis, was readily prepared for thyroidectomy with the use of corticotropin. Thyroidectomy was carried out without incident for the fourth patient, who had asthmatic bronchitis and mild emphysema, after preoperative preparation with cortisone given orally.

REPORT OF CASES

CASE 1.—A Roman Catholic nun, a teacher 43 yr. old, came to the clinic on July 3, 1950, because of asthma. She was found to have gallstones.

Asthma had begun four years previously and at first had followed colds. Later, exertion, chilling, excitement, nervousness and possibly eating chocolate and corn aggravated or precipitated asthma. She coughed and raised clear-to-yellow sputum and experienced a smothering sensation. Asthma occurred daily and was worse at night. The patient also had a nasal allergy,

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From the Division of Medicine, Mayo Clinic.

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with nonseasonal sneezing and blocking. She had undergone polypectomy several times. She had been using epinephrine by nebulizer for relief but had not used epinephrine subcutaneously for six months.

Slight polypoid changes were noted in the middle and superior meatuses of the nose. Both antrums were washed by way of the inferior meatuses, with negative results. Both sides had considerable resistance to injection, suggesting polypoid tissue in the antrums.

An allergic survey carried out with the commoner inhalant and food allergens gave negative results in skin tests. Roentgenograms of the thorax disclosed nothing significant. Differential blood counts revealed eosinophilia of 7 to 11%.

The patient's indigestion consisted of qualitative dyspepsia (intolerance to pork, lettuce, juices, onions and radishes) relieved by antacids and milk. She had some pain at night but said she did not have colic or jaundice. Cholecystography revealed a normally functioning gallbladder, with cholelithiasis. It was advised that cholecystectomy be performed as soon as the asthma could be brought under control. At this time, asthma continued most of the night, and it required frequent inhalations of epinephrine to control it.

Without hospitalizing the patient, the daily intragluteal injection of 100 mg. of cortisone was started on July 9 and was discontinued on July 27. During cortisone therapy the patient experienced a typical gallstone colic on the night of July 10. After discontinuance of cortisone therapy she had a moderate pain in the right lower quadrant of the abdomen on the night of July 30. This subsided in about 12 hr.

Studies of pulmonary function were carried out before and after cortisone therapy by Dr. Henry F. Helmholz, Jr. The most significant change was in the maximal breathing capacity, which on July 8 was 26.72 liters per minute and on July 28 had increased to 39.43 liters per minute. Less significant were the determinations of vital capacity, which increased from 3.09 to 3.27 liters on the aforementioned dates.

The patient's asthma gradually subsided while she was taking cortisone. She was able to lie flat in bed without coughing or wheezing. Cholecystectomy was delayed until August 3, to avoid any possible untoward effects on normal healing. The gallbladder and appendix were removed by Dr. J. T. Priestley, at which time results of exploration of the liver, stomach, duodenum, pancreas, spleen and pelvis were negative. The gallbladder was slightly enlarged; it contained sandy material and two rounded stones 1 cm. in diameter. The common bile duct was explored, but no calculus was encountered. The appendix was chronically inflamed.

The patient's convalescence was uneventful. She had no recurrence of asthma at the time of her dismissal on Aug. 23, 1950.

CASE 2.—A Croatian housewife 53 yr. old came to the clinic on July 25, 1950, because of asthma. It was found that she also had a large incarcerated umbilical hernia. Asthma had begun three years previously, after an acute cold and bronchitis. She had improved after hospitalization elsewhere, but asthma had continued. She was again hospitalized in 1948 and was given penicillin and other drugs. Improvement was noted, but symptoms returned after a week. A third period of hospitalization in the fall of 1948 did not relieve her asthma. In March, 1950, after bronchitis, severe asthma developed. The patient had one to three paroxysms during each 24 hr. Epinephrine had been required for relief of attacks, and the patient apparently had been given morphine for the severer attacks. Her last hospitalization had been on July 5, at which time she had received penicillin, without improvement. She had lost 50 lb. (22.7 kg.) in the last three years, 25 lb. (11.3 kg.) of which had been lost in the last six months before she came to the clinic. She had had chronic nasal congestion for several years. Nasal polyps had been removed in February, 1950.

The patient was admitted to the hospital on July 25, 1950, as an emergency because of her asthma. There was considerable symptomatic improvement after two days of hospitalization and the use of symptomatic remedies. She continued to have asthma, however, and it was not possible to consider repair of the irreducible umbilical hernia because of this.

The use of corticotropin in doses of 20 mg. at 8:00 a. m., 2:00 p. m., and 8:00 p. m. was started on Aug. 2, 1950. On the next day she felt somewhat better, but was still having mild asthma. By August 5, she was feeling much better, was having no paroxysms of asthma but still had a few wheezes in the thorax. The use of all medications other than corticotropin was discontinued on August 5 but was resumed on August 6 because she was again having

asthma. On August 7 corticotropin was given every six hours in doses of 20 mg. On August 10 the chest was entirely clear and the patient was comfortable. An investigation of sinuses revealed some pus, which was removed by washing. The consultant did not feel that surgical attention to the sinuses was necessary. With the complete cessation of asthma, the use of corticotropin was discontinued on August 11, and the patient was scheduled for herniorrhaphy. On August 14 an incarcerated mass of omental fat in the umbilical hernial sac was excised through a transverse elliptic incision. Postoperatively, there was no asthma of any consequence. On August 17 and August 18 epinephrine was used a total of three times only. At the time of dismissal on Aug. 23, 1950, the patient was having no asthma or dyspnea. She was instructed in the self-administration of epinephrine and was given prescriptions for a saturated solution of potassium iodide and for aminophylline to be used rectally if the asthma returned. The avoidance of respiratory irritants of all types was urged.

The estimated normal vital capacity for this patient was 3.4 liters. On Aug. 2, 1950, the vital capacity was 1.73 liters; on August 7, 2.31 liters, and on August 12, 1.09 liters. The maximal breathing capacity on August 2 was 18 liters per minute; on August 7, 27 liters per minute, and on August 12, 40.9 liters per minute.

The patient was readmitted to the hospital on September 11 because of a fluctuating abscess of the anterolateral aspect of the right thigh. Soreness in this area had been noted at the time she had been dismissed from the hospital on August 23. At that time the patient had been advised to use hot packs locally. The area had become abscessed, however. On September 13 it was necessary to carry out incision and drainage of the abscess; 150 cc. of yellow pus containing several old blood clots was evacuated. The patient's convalescence was satisfactory, except for mild asthma, which responded to the use of iodides, aminophylline in rectal suppositories, and a preparation containing ephedrine taken orally.

Case 3.—A housewife 48 yr. old came to the clinic on Nov. 8, 1950, for thyroidectomy which had been advised on previous occasions of her admission to the hospital. Goiter had been present for more than 25 yr. and had appreciably enlarged in the past 10 yr. There was roentgenologic evidence of tracheal compression from the goiter. There was no clinical evidence of hyperthyroidism. Basal metabolic rates taken several times were within normal limits.

Asthma and vasomotor rhinitis had had their onset two years previously, after "virus pneumonia." The nasal symptoms were nonseasonal daily sneezing and running and blocking of the nose. The asthma was becoming progressively worse.

The patient was admitted to the hospital and given aminophylline intravenously with solution of dextrose. Iodides and an ephedrine preparation were given orally. On the third hospital day, the administration of corticotropin was begun and the use of other medications was discontinued. On November 11 the patient received 20 mg. of corticotropin every six hours, and on each of the following two days, 10 mg. every six hours. On the fourth and last day she received a tapering-off dose of 5 mg. every six hours. She received a total of 180 mg. in four days.

On the first day of treatment the nose was more nearly open. Eighteen hours later the nasal symptoms had abated about 90% and the appearance of the nasal mucosa was almost normal.

The patient's chest had very few wheezes after the second day of treatment with corticotropin. On November 14 the chest was clear, and the patient was permitted to leave the hospital.

After a precautionary delay of six days thyroidectomy was carried out without incident. Seventy-four grams of tissue was removed. The pathologist found multiple calcareous hemorrhagic degenerating colloid and fetal adenomas in a colloid thyroid.

Results of skin tests with common air-borne and food antigens were negative on two occasions. Roentgenograms of the thorax likewise yielded negative results. It is of passing interest to note that this patient had no evidence of recurrence of a grade 2 adenocarcinoma of the left kidney which had been removed on Nov. 1, 1948.

The patient's convalescence after thyroidectomy was normal. There was more than average drainage from the incision, but she was dismissed from our care on Nov. 30, 1950, the 16th postoperative day. At that time a few asthmatic wheezes could be heard, but frank asthma was not present at the time of her dismissal.

CASE 4.—A housewife 48 yr. old experienced a persistent, moderately productive cough after pneumonia in the fall of 1949. The first asthmatic symptoms had appeared briefly in March, 1950, and each month from July to December she experienced attacks of asthma requiring hospitalization for periods varying from three to eight days. She lost 45 lb. (20.4 kg.) over an eight-month period. She had been given corticotropin in July, 1950, with marked abatement of symptoms within four to six hours. Subsequently, when it was given during each monthly hospitalization, relief occurred but was delayed for 36 to 48 hr. She had also inhaled penicillin dust and practiced postural drainage. The sputum was described as "thick" and containing "pearls" or mucous plugs or casts; occasionally it was yellow. It was not typical of the sputum of bronchiectasis. The unsatisfactory course of the patient's illness was associated with increasing nervousness. After a tooth had been removed in September, 1950, she had remained in bed three months, even when not having asthma, because of weakness and lassitude.

On admission to the clinic on Jan. 29, 1951, the patient weighed 87 lb. (39.5 kg.) without clothes. She was hospitalized for symptomatic treatment and examination. The blood pressure was 134 systolic and 96 diastolic, expressed in millimeters of mercury, the pulse rate was 100 and the temperature 98.6 F. The lungs yielded sibilant and sonorous rales, with prolonged, difficult expiration. A soft adenomatous goiter estimated to be 30 to 40 gm. in weight was present. Roentgenograms of the thorax showed evidence of slight emphysema and residual iodized oil in both lungs from previous bronchography. Leucocytes numbered 12,100 per cubic millimeter of blood; 65% were neutrophils and 9.5% were eosinophils. Results of intradermal skin tests with a series of common inhalant antigens were negative, as were results of examination of the nose and sinuses. Epinephrine, aminophylline used rectally, iodides, and nebulized penicillin controlled the asthma so that bronchoscopy could be carried out on Feb. 2, 1951. At this time a moderate degree of inflammatory reaction was noted throughout the bronchial tree. Mucoid secretion was present. Bronchial stenosis could not be demonstrated. There was no bronchial spasm during the time of the examination.

There was no clinical evidence of a toxic goiter. The basal metabolic rate was +11 on two occasions. Thyroidectomy was advised for prophylaxis. Because the patient was still having considerable nocturnal asthma, too much to consider thyroidectomy, she was given cortisone orally on February 11. She took 25 mg. every six hours. The asthma subsided gradually; on February 15 the chest was entirely clear and the patient felt well. The use of cortisone was discontinued on February 16, the patient having taken a total of 575 mg.

On February 20, subtotal thyroidectomy was carried out. Both lobes of the thyroid gland were enlarged about three times normal size. The pathologist reported the weight of the specimen as 22 gm. It contained multiple degenerating colloid and fetal adenomas.

Postoperatively, the patient's chest remained clear. She left the hospital on the fifth postoperative day and returned home on March 2, 1951.

For this patient to remain well, it will be necessary for her to avoid all types of respiratory irritants, especially colds, and to control her tendency toward overcoughing. She had the mistaken idea that it was necessary for her to cough out mucus as fast as it formed in her air passages. The nervous factors so prominent during the early phases of her treatment had practically disappeared at the time of her dismissal.

COMMENT

Since cortisone and corticotropin (ACTH) had been shown experimentally [2] to retard fibroblastic reaction, it was felt safer to discontinue the administration of

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either preparation for a few days before surgical treatment. In the first instance the interval before operation was one week in the case of cortisone and three and six days in the case of corticotropin. Thyroidectomy was carried out four days after the oral administration of cortisone was discontinued in the last case. There remains some question about how important or necessary such a delay actually is, inasmuch as relatively huge doses of cortisone and corticotropin were necessary to retard fibroblastic reaction experimentally.

The only complication which perhaps could be attributed to the medication occurred in the second case. The abscess occurred at the site of the intramuscular injection of corticotropin; formation of the abscess probably was the consequence of a breakdown in technic, rather than the effect of corticotropin on fibroblastic reaction.

The administration of cortisone and corticotropin in the preoperative preparation of patients who have asthma resistant to usual forms of treatment proved effective and valuable for the four patients so treated.

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TUBERCULOSIS ORIGINATING FROM CONTAMINATED SUTURE MATERIALS AND PLASTICS

An Experimental Study

H. J. CORPER, M.D., Ph.D.
AND
MAURICE L. COHN, Ph.D.
DENVER

AN EARLY axiom in tuberculosis warned against opening or manipulating tuberculous foci. In vitro, the mammalian tubercle bacillus assumes the aspects of a self-limited grower on the surface of solid nutrient mediums as well as on the surface of (and submerged in) liquid mediums.[1] The spread of growth in vitro or in vivo, therefore, to some extent appears to be movement from external sources and not inherent in the bacilli themselves. Many modern procedures to benefit the patient take full cognizance of these facts and yet at times they are overlooked, as in surgical intervention, in which, unfortunately, evaluation is difficult or impossible. Earlier investigations demonstrated the detrimental effect of certain foreign materials [2] and spreading agents [3] on tubercle bacilli and on tuberculosis. With increasing use of surgical procedures, it becomes important to determine the effect of simple traumatism on the spread of tuberculosis, the significance of the surgical suture in spreading this disease in certain circumstances, and the possibility of preventing this hazard. In addition, the present tendency to use solid materials such as plastic balls and sponges or sheets for plombage also brings this problem into closer focus.[4]

To determine the effect of tuberculous contamination of surgical sutures and whether such contamination has more or less effect than the spread of the bacilli themselves, a series of experiments was planned to disclose the quantitative nature of such effects and to prevent obvious error in interpretation such as might be made if the quantitative aspects were ignored. Our previous experience taught that the

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This investigation was aided by a gift from Morton May in memory of Florence G. May.

From the Research Department, National Jewish Hospital at Denver, and the University of Colorado School of Medicine.

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2. Vidal, C. B.: The Effects of Adding Various Substances to Suspensions of Tubercle Bacilli in Experimental Infection, Am. Rev. Tuberc. **32**:601-603, 1935.

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amount of tubercle bacilli introduced could be controlled fairly accurately on a weight basis, and the use of the same bacillary strain and culture insured fairly exact evaluation. To prevent possible error in the quantitative aspects, instead of the sutures being drawn through the skin, which could remove bacilli especially from the smooth nonabsorbing surfaces of some suture materials, they were introduced by first inserting a large-gauge needle (about 14 to 16 gauge) into the skin for a definite length and the suture containing the bacilli was carefully threaded through this, after which the suture was held in place while the needle was carefully

TABLE 1.—*Surgical Ligatures in Association with Virulent Human Tubercle Bacilli and the Dissemination of Tuberculosis in the Guinea Pig*

No. and Description	Tubing Fluid	Amount of Tubercle Bacilli in Mg. Adhered per Inch of Material *	In Vitro Cultures of Materials †	Abscess Formation, Average Time in Days	Time of Local Gland Appearance and Size at Autopsy	Average Amount of Tuberculosis at 35 Days ‡
No. 1 Catgut, intestinal, boilable	Xylol	0.0008	0 + †	None	1 wk.+	± ‡
No. 2 Catgut, intestinal, boilable, washed with carbon tetrachloride	Xylol	0.0004	0 +	21	1 wk.++	++
No. 3 Surgical gut U.S.P., medium chromic	Ethyl alcohol, 70%; isopropyl alcohol, 20%; phenyl mercuric benzoate, 0.025%; water to 100%	0.0010	0 +	12	1 wk.+++	+++
No. 4 Surgical gut U.S.P., medium chromic, washed with sterile water	Ethyl alcohol, 70%; isopropyl alcohol, 20%; phenyl mercuric benzoate, 0.025%; water to 100%	0.0010	0 +	11	1 wk.+++	++++
No. 5 Surgical silk U.S.P., eye-suture	Liquid petrolatum	0.0008	++	11	1 wk.+++	+++
No. 6 Surgical silk U.S.P., eye-suture, washed with carbon tetrachloride	Liquid petrolatum	0.0008	++	11	1 wk.+++	+++
No. 7 § Catgut U.S.P., nonboilable, medium chromic	95% alcohol, 0.05% potassium mercuric iodide	0.0007	0 +	None	1 wk.±	0
No. 8 Catgut U.S.P., nonboilable, medium chromic, washed with sterile water	95% alcohol, 0.05% potassium mercuric iodide	0.0002	0 +	11	1 wk.+	+
Infection controls, 0.001 mg. #4008 subcutaneously	.....	.....	....	None	2 wk.±	0

* A fine bacillary suspension was used containing 1 mg. of virulent human tubercle bacilli #4008 per cubic centimeter of 0.9% sodium chloride solution.

† The markings designate the results of the culture on delicate egg yolk medium and are given as the absence (0) or presence (+) of growth in close proximity to the material, the second mark indicating the growth at a distance from the material tested.

‡ The amount of general organic tuberculosis in the guinea pig at autopsy is arbitrarily recorded from 0, indicating no visible macroscopic disease, to ++++, indicating a generalized disease involving all the important organs.

§ Sutures still in situ at time of killing guinea pigs.

withdrawn. The ends of suture projecting beyond the points of insertion were then trimmed off so that the suture of definite length could retract sufficiently back of the incision to prevent surface infection as far as possible. A number of suture materials were used, including catgut (intestinal), surgical gut, surgical silk, and nonboilable chromic gut. In all cases all the liquid was removed and the sutures were washed with solvent to remove this liquid as far as possible. As a control, cultures were also made on a good diagnostic egg yolk medium capable of disclosing

small plants of mammalian tubercle bacilli. The results of this study with sutures impregnated with definite quantities of virulent human tubercle bacilli (#4008) are recorded in Table 1.

Table 1 presents rather striking effects in that suture materials impregnated with approximately 0.0002 to 0.001 mg. of virulent human tubercle bacilli not only definitely aggravate the local subcutaneous tuberculous involvement in the guinea pig but also tend to spread the generalized disease in these animals compared with control animals given subcutaneous injections of the same amount of the same tubercle bacilli. It was interesting to note also that certain types of antiseptic materials, if permitted to remain in or on the suture material, tended to destroy the bacilli. This was true of xylol and potassium mercuric iodide.

Recent interest in modern plastics made it desirable to study these in addition to the sutures, especially in view of their striking effects in aggravating tuberculosis. The substances studied, quantitatively impregnated with virulent tubercle bacilli, were lucite,® polyethylene sheets, vinyl sponge, nylon (polyamine resin), and glass

TABLE 2.—*Effect on Tuberculosis Resulting from Plastic Materials Associated with Virulent Human Tubercle Bacilli*

Material	Amount of Tubercle Bacilli in Mg. Adhering per Inch of Material *	Abscess Formation, Average Time in Days	Time of Local Gland Appearance and Size at Autopsy	Average Amount of Tuberculosis at 35 Days †
Lucite (methyl methacrylate)	0.004	12	1 wk.+++	+++
Glass fiber	0.026	7	1 wk.+++	++++
Polyethylene sheets	0.019	7	1 wk.+++	++++
Vinyl sponge	0.027	7	1 wk.+++	+++
Nylon (polyamine resin)	0.059	7	1 wk.+++	++++
Infection control, 0.01 mg. #4008 subcutaneously	.....	None	1 wk.+	+
Infection control, 0.001 mg. #4008 subcutaneously	.....	None	2 wk.+	+

* Cultures were positive and in close contact with plastic materials, indicating absence of any in vitro retardant effects of these materials.

† The amount of general tuberculosis in the guinea pigs at autopsy is graded arbitrarily from 0, indicating no visible organic disease, to ++++, indicating a generalized organic involvement of the usual organs.

fiber, the latter usually considered an inert hard substance. The results of these experiments are recorded in Table 2.

Table 2 indicates that, like the suture materials, lucite,® polyethylene sheets, vinyl sponge, and nylon exerted a marked tendency toward the development of tuberculosis at the site of contact and affected the extent of tuberculosis in the local lymph glands as well as the organic involvement. It is obvious that this fact should be considered seriously, as already prescribed by certain cautious surgeons, and tuberculous tissues avoided during operative procedures by means of sutures or other materials such as are advocated for plombage. Although these observations were made in nonimmune guinea pigs, in which there is considerable susceptibility toward virulent human tubercle bacilli, it appears obvious that they apply, to a definite though more limited extent, to human beings, in whom such exacting controlled experiments would be impossible. The striking regularity of the findings here reported emphasizes their validity, and they concur with previous observations on human beings.

SUMMARY AND CONCLUSIONS

Tuberculous infection resulting from the introduction of virulent human tubercle bacilli into the subcutaneous tissues is markedly aggravated by association with suture materials in regard to both speed of development and spread of the disease. This effect was prevented to some extent by certain preservatives used with these suture materials.

The aggravation and spread of the tuberculous infection was also pronounced in association with lucite, polyethylene, vinyl sponge, and nylon, as well as glass fiber. This action appears to be dependent on the phenomenon of a foreign body aggravation of the tuberculous infection.

On the basis of these experiments, precautionary measures appear especially warranted to avoid contamination with suture and plastics used surgically by contact with tuberculous tissues or foci.

THYROIDITIS

CARL P. SCHLICKE, M.D.
SPOKANE, WASH.

THYROIDITIS is a little known and infrequently recognized disease process. As recently as 1935 Cochrane and Nowak [1] wrote: "It is no exaggeration to say that thyroiditis as an entity is unknown to the average internist and surgeon." Patterson and Starkey,[2] after a study of 24 cases of chronic thyroiditis in 1948, were amazed at the low incidence of correct preoperative diagnosis. Riedel [3] described ligneous thyroiditis in 1896, Hashimoto [3] described struma lymphomatosa in 1912, and in recent years Crile [5] has written extensively about subacute thyroiditis. It is a little difficult to understand why such unfamiliarity with the condition exists.

Among 7,045 patients with thyroid disease seen at the Cleveland Clinic between 1936 and 1947, 143 cases of thyroiditis were encountered.[6] A similar ratio (24 in 1,595) is reported from the Jewish Hospital in Brooklyn.[7] At the Roosevelt Hospital in New York 1 in 100 operations on the thyroid gland was for Hashimoto's disease, with Riedel's struma only slightly less frequent.[2] My colleagues and I were surprised at the number of cases of thyroiditis which came under our observation at the Rockwood Clinic in a three and one-half year period beginning June, 1947, and ending December, 1950. It was felt that a report of these cases might be of interest to others.

CLASSIFICATION OF THYROIDITIS AND DISCUSSION OF CASES

Thyroiditis may occur in glands previously normal or goitrous. It may be focal, spreading, or diffuse. A workable classification of thyroiditis appears in the accompanying table.

From the Surgical Service, Rockwood Clinic.

Read at the annual meeting of the Spokane Surgical Society, April 21, 1951.

1. Cochrane, R. C., and Nowak, S. J. G.: Acute Thyroiditis with Report of Ten Cases, New England J. Med. **210**:935-942 (Aug.) 1935.

2. Patterson, H., and Starkey, G.: Clinical Aspects of Chronic Thyroiditis, Ann. Surg. **128**:756-768 (Aug.) 1948.

3. Cited by Brayton, D. F.: Subacute and Chronic Nonsuppurative Thyroiditis, West J. Surg. **56**:417-423 (July) 1948.

4. Footnote deleted.

5. (*a*) Crile, G., Jr.: Thyroiditis, Ann. Surg. **127**:640-654 (April) 1948; (*b*) Treatment of Thyroiditis, Arch. Surg. **57**:443-449 (Oct.) 1948; (*c*) Practical Aspects of Thyroid Disease, Philadelphia, W. B. Saunders Company, 1950.

6. Osmond, J. D., Jr., and Portmann, U. V.: Subacute (Pseudotuberculous, Giant Cell) Thyroiditis and Its Treatment, Am. J. Roentgenol. **61**:826-829 (June) 1949.

7. Lasser, R. P., and Grayzell, D. M.: Subacute Thyroiditis, Struma Fibrosa, Struma Lymphomatosa: Clinical Pathologic Study, J. M. Sc. **217**:518-529 (May) 1949.

Acute Thyroiditis.—Acute thyroiditis may be suppurative or nonsuppurative and may be bacterial in origin. No such cases were encountered in this series.

Subacute Thyroiditis.—Subacute thyroiditis is the commonest form. This is sometimes called pseudotuberculous or giant-cell thyroiditis. The etiology of this condition is unknown, but studies by others have failed to reveal tubercle bacilli or other bacteria, and a virus may be implicated. It is not unlike acute parotitis in many of its manifestations. There were seven such cases in our series.

The onset of the disease is sudden and may occur at any age. Our patients ranged in age from 19 to 64 yr., with an average age of 38.7 yr. It is commoner in women than in men, the ratio being six to one in our series. It is more likely to attack a normal gland (six patients) than an adenomatous one (one patient) and has seldom been reported in hyperplastic glands. The disease may follow an acute upper respiratory infection, although we saw only one instance of this. The duration of symptoms, when our patients were first seen, ranged from one to four

Classification of Thyroiditis

I. Acute
  A. Suppurative (bacterial)
  B. Nonsuppurative
II. Subacute (pseudotuberculous; giant cell)
III. Chronic
  A. Specific
    1. Tuberculous
    2. Syphilitic
    3. Actinomycotic
  B. Nonspecific
    1. Struma lymphomatosa (nonfibrosing: Hashimoto)
    2. Struma fibrosa (ligneous: Riedel)
    3. Unclassified or intermediate (deQuervain's, etc.)
    4. Lymphoid infiltration in hyperthyroidism

weeks, with an average of two weeks. Laboratory findings are usually not remarkable except for an increased sedimentation rate.

The symptomatology is characteristic. All patients experienced moderate to severe pain in the region of the thyroid gland, and the pain often radiated to the ears or teeth. Moderate to exquisite tenderness was present in all patients. Some of them held the neck flexed to relieve pressure on the gland. Swelling was generalized in six cases, though not always symmetrical, and involved only the right lobe in one case. Induration accompanied swelling and was often stony-hard. All patients complained of sore throat, three of dysphagia. Redness and local heat were present over three glands. Five of the patients had a low grade fever of one to four or five degrees, although recently we saw a patient in consultation who had a temperature of 105 F. Symptoms of toxemia, sweats, weakness, malaise, exhaustion, nervousness, irritability and emotional instability were prominent features. Some of the patients appeared stimulated, but this was a toxic and not a hyperthyroid manifestation. One patient had a persistent cough, and one displayed the Delphian node described by Cope.[8] Weight loss occurred in three cases, one patient losing 18 lb. (8.2 kg.).

8. Cope, O., cited by Means, J. H.: The Thyroid and Its Diseases, ed. 2, Philadelphia, J. B. Lippincott Company, 1948, p. 571.

The diagnosis of subacute thyroiditis is usually self-evident. The patient, of course, often thinks he has simply a sore throat, and if one does not palpate his neck, one may concur in his opinion. Sudden enlargement of the gland may be due to hemorrhage into an adenoma. When this occurs, the gland may become tender and hard, but systemic manifestations are lacking, the process is pretty well localized, and local heat seldom is present. When toxic symptoms predominate, an acute hyperthyroid state may be suspected, but the absence of local inflammatory signs and the elevated metabolic rate serve to differentiate this condition. The only local condition which may mimic subacute thyroiditis is cellulitis of the neck; a careful examination will usually indicate the diffuse nature of the latter and disclose enlarged, tender, cervical lymph nodes.

The treatment of subacute thyroiditis depends on the severity of the disease. In mild cases symptomatic therapy, with hot or cold packs, analgesics, sedatives and rest, is all that is necessary. Such therapy was employed as the sole form of treatment in one of our cases and as an adjunct in all. In severe cases the patient is so sick and in such pain and misery that one casts about for additional help. Antibiotic and chemotherapeutic agents have not proved helpful in the hands of others. We used penicillin in two cases, with doubtful benefit. Strong iodine solution (Lugol's solution) has been tried empirically without success. At the Cleveland Clinic roentgen therapy has been employed since 1933 and is regarded there as the best form of treatment. The results in 55 cases were reported by Osmond and Portmann.[6] Forty patients were cured with one course of treatment, and six were improved after one course and cured by a second course of treatment. The treatment consisted of administration of 100 to 150 r every other day for four to six exposures. It has been suggested that the roentgen rays may inactivate the causative virus or the effect may be a nonspecific one on the inflammatory process itself. Only one of our patients received roentgen ray therapy. This patient was given six treatments of 125 r each over a period of three weeks. She felt better after her first treatment but the thyroid gland continued toxic and tender. She had a rather marked exacerbation of all the signs and symptoms about the time the treatments were discontinued. At this time administration of penicillin was started, and she improved rapidly during the following week. Whether this improvement was due to the penicillin or to the delayed results of roentgen ray therapy would be hard to say.

None of our patients was operated on during the subacute phase; hence we have no pathologic material to present. Surgical intervention allegedly arrests the inflammatory process and has been carried out with surprising frequency according to some reports. This is unjustifiably heroic therapy in a self-limited disease. All that can be said for it is that it has given us a picture of the gross pathologic findings, which consist of a white, swollen brittle avascular nonadherent gland. However, Crile has obtained information regarding the microscopic picture with far less discomfiture to the patient by employing a Silverman liver biopsy needle and removing a specimen of the gland for study.[5e] In the main, the findings consist of fibrosis, especially in the connective-tissue partitions, foci of small follicles with reduced or absent colloid, infiltration with lymphocytes, plasma cells, occasional polymorphonuclear leucocytes, foreign body giant cells and focal accumulation of

histiocytes. The giant cells represent a response to phagocytosis of degenerating colloid by wandering cells. Pseudotubercles may be formed. One of our patients who had a preexisting adenomatous goiter was subjected to thyroidectomy five months after the subacute thyroiditis had subsided. At this time some residual fibrosis and leucocytic infiltration was still present.

In 1945, after giving thiouracil to 10 patients with subacute thyroiditis, King [9] was so impressed with its value that he felt it could be considered a specific when administration was started early in the course of the disease. Cantwell [10] and others have contributed favorable reports after using the same drugs. We used thiouracil, 0.2 gm. three times daily, on one patient and propylthiouracil, 50 mg. three times daily, on four patients. The pharmacological reason for any possible beneficial effects is obscure, although suppression of colloid formation may be a factor.

Thyroiditis is a self-limited condition. It usually runs a course of from six weeks to six months, ultimately subsiding without impairing thyroid function. It is difficult to evaluate therapy in a self-limited condition. Furthermore, a series such as ours is too small to prove anything about the relative values of different forms of treatment. However, the disease ran a shorter course in our patients than one would ordinarily expect. Subjective improvement and disappearance of fever occurred in the first week in five patients and by the second week in the sixth patient, and only in one case was improvement delayed until the fifth week. In all cases tenderness and swelling disappeared in one to three months. One cannot but wonder whether the agents employed played a part in this disappearance. Their effects were not instantaneous or dramatic, but the over-all picture is better than one would ordinarily anticipate.

Chronic Thyroiditis.—Chronic thyroiditis may be specific or nonspecific. Isolated cases due to tuberculosis, syphilis and actinomycosis have been reported but are so rare as to constitute medical curiosities. Nonspecific, chronic thyroiditis is seen most commonly as a lymphoid infiltration, occurring in hyperplastic glands. In this form it is of interest chiefly to surgeons, who have learned that when thyroidectomy is carried out in its presence it must be conservative or myxedema will result. Both normal thyroids and endemic goiters exhibit remarkable regenerative powers. Even removal of a nodular goiter with or without hyperthyroidism is seldom followed by hypothyroidism. But after removal of a diffuse goiter with lymphoid infiltration, failure of function of the thyroid remnants is not uncommon.[5c]

Clinically, there are two principal varieties of chronic thyroiditis: the form described by Riedel (ligneous thyroiditis)[11] and the form described by Hashimoto (struma lymphomatosa). Between these two there are numerous unclassified and intermediate varieties such as the one described by deQuervain.[3] Ewing [13] was of

9. King, B. T., and Rosselini, L. V.: Treatment of Acute Thyroiditis with Thiouracil: Preliminary Report, J. A. M. A. **129**:267-268 (Sept. 22) 1945.

10. Cantwell, R. C.: Thiouracil in Acute Thyroiditis, Ann. Int. Med. **29**:730-732 (Oct.) 1948.

11. Hashimoto, H., cited by Brayton, D. F.: Subacute and Chronic Nonsuppurative Thyroiditis, West. J. Surg. **56**:417-423 (July) 1948.

12. Footnote deleted.

13. Ewing, J.: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922.

the opinion that Hashimoto and Riedel were discussing early and late forms of the same disease. Others have attempted to trace the development of these two conditions from the so-called Grave's constitution with or without thyrotoxicosis (Rabson and Arata)[14] and from subacute thyroiditis, with ligneous thyroiditis representing the end stage. Graham and McCullagh [15] noted certain fundamental differences and pointed out that the two conditions were actually dissimilar and were disease entities rather than progressive phases of the same process. As our series is too small to illustrate these differences except in the pathologic findings, it may be well briefly to review them. Hashimoto's disease tends to occur in an older age group. It is almost exclusively a disease of women. The symptoms are of longer duration. Involvement of the gland is always bilateral. Pressure phenomena are uncommon. Riedel's struma occurs at a slightly earlier age. Twenty to 40% of the patients are men. Involvement may be limited to one lobe in almost one-half of the cases, and adenomas may be present. Pressure symptoms are more pronounced than in any other disorder of the thyroid gland. Hashimoto's disease is thought by some to represent a systemic disorder, sometimes associated with achlorhydria and generalized lymphoid hyperplasia, whereas Riedel's struma is a chronic, proliferative, fibrosing, inflammatory process. Both diseases are progressive and may go on to ultimate destruction of the gland, in the one case by the production of lymphoid and fibrous tissue and in the other by extensive fibrosis, with resulting myxedema. Riedel's struma may go on to involve the parathyroids, the recurrent laryngeal nerves and the other tissues in the vicinity of the thyroid gland even if the patient is so fortunate as to escape choking to death.

We have had six patients with chronic thyroiditis. The ages range from 38 to 71, with a mean of 53.2 yr. All patients were women. In only one patient was the goiter the chief complaint. In three patients operation was advised because examination revealed what was thought to be an adenomatous goiter with mild toxicity and with associated pressure symptoms in two. One of these patients, aged 42, had severe hypertension. Another, aged 64, suffered from uncontrolled diabetes, generalized arteriosclerosis and arteriosclerotic heart disease. In three patients operation was advised, because of the hard asymmetrical character of the gland which suggested the possibility of malignancy. Only once was the possibility of an inflammatory process considered preoperatively.

All patients were subjected to subtotal thyroidectomy. There were no deaths. In four cases thyroiditis was suspected at operation because the glands were found to be uniformly enlarged, lobulated, nonadherent, pale grayish pink, firm and avascular. Slight enlargement of the regional lymph nodes was noted in two instances. The pathologist reported Hashimoto's disease in two of these cases, deQuervain's disease in one, and unclassified thyroiditis in one. Conservative resection was carried out. In two patients the gland was stony hard. In one of these thyroiditis was suspected at operation, and conservative resection was carried out. In the other, malignancy was suspected because of the predominantly right-sided

14. Rabson, S. M., and Arata, J. E.: Hashimoto's and Riedel's Strumas and Lymphadenoid Goiter, Am. J. Clin. Path. **19**:750-764 (Aug.) 1949.

15. Graham, A., and McCullagh, E. P.: Atrophy and Fibrosis Associated with Lymphoid Tissue in Thyroid: Struma Lymphomatosa (Hashimoto), Arch. Surg. **22**:548-567 (April) 1931.

involvement, with extensive adhesions to the surrounding tissues that necessitated removal of the overlying ribbon muscles which could not be separated from the gland, and a complete lobectomy was carried out on the right, with conservative resection of the remaining, slightly nodular left lobe. The pathologist reported Riedel's struma in both of these cases.

Microscopic study of the Hashimoto type of glands showed degeneration of epithelial elements, distortion of the architecture of the gland and its acini, and extensive lymphoid infiltration. Lymphoid follicles with germinal centers were present, and some fibrosis was to be seen. The sections taken from the Riedel type of glands showed no normal thyroid tissue present. Extensive fibrosis and scarring predominated. Many acini were distorted or destroyed, and in some areas only small islets of recognizable thyroid tissue were present. Mild lymphocytic infiltration was present. Sections of one of the unclassified glands showed involutional changes of epithelial elements, with increased connective tissue and lymphocytic infiltration of the stroma and occasional lymph follicles with germinal centers. The gland from the remaining patient exhibited complete destruction by an infiltrate of small lymphocytes and fibrosis. Numerous giant cells were present. The pathologist thought that these findings represented deQuervain's disease.

From the standpoint of treatment, it is unfortunate that our diagnostic acumen is not greater. The treatment of chronic thyroiditis by operation is empiric. Morbidity in most reported series is high. Hypothyroidism is almost sure to follow, as it did in four of our six cases. To be sure, surgical intervention seems to arrest the progress of the disease for reasons which we do not understand, and in cases of Riedel's struma with tracheal and esophageal compression it may be lifesaving. Yet there are undoubtedly cases of Riedel's struma in which, if the possibility of malignancy could be excluded, operation would be unnecessary. Furthermore, Crile has shown that Hashimoto's disease responds satisfactorily to roentgen therapy.[5a] In two of his patients this was carried out after he established the diagnosis by needle biopsy and the need for operation was obviated. X-rays, unfortunately, are completely ineffective in the management of Riedel's struma.

COMMENT

The various forms of thyroiditis are a strange group of diseases. The etiology is unknown. The terminology and classification are confused, and concepts of pathogenesis are in controversy. Recognition is infrequent although the incidence is higher than is generally appreciated. Women are afflicted far more often than men, although the ratio of women to men was found to be only three to one in the rest of our cases of thyroid disease coming to surgery. Subacute thyroiditis may be a virus disease. Roentgen therapy and administration of thiourates apparently shorten its course, but in any event it is a self-limited process. Surgical intervention is unwarranted in its management. Struma lymphomatosa appears to represent a marked overgrowth of the lymphoid tissue frequently encountered in the thyroid gland. This tissue is said to be radiosensitive, and more liberal use of a biopsy needle may eliminate the need for dangerous and unsatisfactory operations in some cases. Surgical operation is still the only treatment we have for ligneous thyroiditis, but when performed it should be as conservative as possible. Sometimes simple

decompression of the trachea is all that is necessary, or it may be possible to shell out a degenerating adenoma which forms a central core. Why these various forms of treatment seem to be beneficial is as obscure as are the forms of disease themselves.

SUMMARY

Thirteen cases of thyroiditis have been presented. Seven patients were suffering with subacute thyroiditis. Therapy included the use of thiourates, roentgen rays, and antibiotics. Six patients had chronic thyroiditis; two of these were considered to have Hashimoto's disease and two to have Riedel's struma, and two of them fell into an unclassified group. Conservation thyroidectomy was carried out in these six patients.

CHALLENGE OF THE FOREIGN BODY

EDWIN P. LEHMAN, M.D.
CHARLOTTESVILLE, VA.

IT IS RECORDED that William J. Mayo, in recalling the early days at Rochester, said of himself and his equally illustrious brother: "We were very green and we knew it." The latter half of this sentence furnishes one key to their accomplishments. When the invitation was received to give this lecture, the thought occurred to me that perhaps I might best fulfil the purpose of its distinguished founder were I to present a subject the fundamental knowledge of which is still in bud. Surgeons are not unaware of the extent of ignorance on this subject; therein lies the hope of the future, just as their awareness of ignorance determined in part the growth in skill and knowledge of the Mayo brothers. The subject which I have chosen is the reaction of tissues to foreign bodies. My hope is to define within the limits of my capacity the boundaries of our present knowledge of the problem.

One need not emphasize the importance of the foreign body in surgery. The commonest maneuver next to the division of tissue is the deliberate introduction into the body of foreign materials. Although the accidentally introduced foreign body may teach us something about the behavior of tissue in contact with various substances, the problem that concerns us primarily is that of the deliberately introduced foreign body, including not only the suture and the ligature but also the drain and the prosthesis. It is interesting that much of our knowledge of the behavior of tissues in contact with foreign bodies is based on empirical observations in both animal and man, observations which, as will be pointed out later, are often poorly controlled. It is my hope to bring the relatively meager body of fundamental information together and thereby to define what we do not know.

HISTORY

The history of the deliberate introduction of foreign bodies goes back to the most remote of surgical records. Let us briefly tread that familiar path. Much of the earliest history is concerned with the ligature and the suture. However, the tent and the seton are also recorded in the dawn of surgery. Hippocrates speaks of the tent. Melle [1] states that perhaps the earliest record of the ligature is found in the Edwin Smith papyrus of Egypt, the date of which is some 2,000 years B. C. Susruta in India is said to have employed cotton, horsehair and animal ligaments for ligatures some half a century before Christ. Beginning with about the time of Christ, there are scattered references in the medical literature up to the 16th century, when Paré's great contribution was made. Among the dozen or fifteen writers

The William J. Mayo Lecture, University of Michigan, May 16, 1951.
From the School of Surgery, University of Virginia Department of Medicine.

1. Melle, G. J.: The Early History of the Ligature, South African M. J. 8:290, 1934.

who recorded the use of the ligature were Antyllus and Rhazes. These names are picked out because they reported the use of catgut. It is probable that this was only because catgut was an easily available thread employed in the construction of musical instruments, including the harp, and not because of its absorbable nature. The contribution of Paré is known to all of us, and there is not the time to repeat this interesting story. We must remember only that the nature of the foreign material introduced was of no importance so long as its introduction was uniformly associated with infection.

Before Lister's time the necessity to allow a long end of a ligature to protrude from the wound in order to be sure that no foreign material was left therein is a matter of historical record. One must recall the obvious relief of the surgeon when the ligature came away without secondary hemorrhage. When Lister first demonstrated the possibility under his antiseptic regimen of cutting both ends of a ligature short and closing the wound over them without the occurrence of infection or secondary hemorrhage and without discharge of the ligature from the wound, the nature of the foreign material itself first became a matter of primary importance. One must not forget to mention the additional contributions of Halsted in adding to our knowledge of a buried foreign body and of the technical conditions under which burial is safe. With this brief comment on centuries of slow progress, we can now turn to the problem as it is presented today.

"TISSUE TOLERANCE"

It is clear that any discussion of the tolerance of tissue for foreign material must be based on the assumption that infection is absent. Gross infection is easy to recognize, but minor degrees of contamination by bacteria, promptly controlled without resulting gross infection, are not easy to measure in experimental studies. And yet, the minimal inflammatory reaction accompanying the destruction of undetermined bacterial contamination may modify the extent and the quality of the tissue reaction to the foreign material itself. It must be recognized in all studies of the foreign body reaction that this indeterminate factor may be present. With this reservation always in mind, let us try to define what is meant by "tissue tolerance" for foreign bodies.

It can be said that almost without exception the introduction of any solid or oily foreign body will cause some reaction in the tissue, ranging from increased enzymatic action without obvious cellular response to excessive fibroplasia and giant cell formation. It can further be said that a foreign body not promptly removed by enzymes will create a cellular response, the end result of which often is a capsule of fibrous tissue around the foreign body. Unremoved foreign bodies are generally walled off from the living organism by the development of scar tissue. If the period of inflammation that precedes repair is short, the development of new tissue slight and the resulting capsule thin, one speaks of the foreign body as being "well tolerated." If, on the other hand, the inflammatory and repair reactions are intense and the resulting capsule thick or if a continuing building up of new tissue occurs, we say that the foreign body is "not well tolerated." In spite of the surgical slang phrases "wet healing" and "dry healing,"[2] it is important to recognize that

2. Gage, I. M., and Lyons, C.: Suture Materials and Their Use, S. Clin. North America **29**:1565, 1949.

all healing is "wet healing" and that the differences are only in degree. For most of the purposes of this discussion, therefore, the problem is fundamentally quantitative. This is a simple conception, but the classification in specific instances as to the degree of toleration may be difficult. Histological comparisons are always subjective; gross differences may be easily recognized but minor differences may be missed or variously interpreted.

There has been a large amount of descriptive and comparative histological study of the foreign body reaction. As has been said, the quality of this reaction is not the phase of the problem with which this discussion is concerned, except as may be noted in one or two specific instances. No attempt, therefore, is made to present the basic pathologic process. The literature is replete with information about everything from the mechanism of the inflammatory process to the origin of the fibroblast and the giant cell without full agreement between pathologists on the answers to many questions. To avoid being led into the byways of pathology, let us accept the commonplace knowledge of tissue reaction to a foreign body and let us state that we are primarily interested in the degree of reaction a foreign body causes and the nature of the mechanisms which determine that degree. At the same time it must be realized that the minutiae of tissue behavior, including the action and interaction of the biochemical processes of living cells, must in the end be the clue to the answers of the questions we would ask.

THE PROBLEM

Knowledge of the morphological behavior of tissue in contact with many types of foreign materials has been obtained by empirical observations in animals and man. Relatively little has been done to find out why differences occur. As a beginning in defining the problem, I shall first list the variables that may play a part in the evocation of the tissue response to a foreign body and that may befog the clarity of experimental studies, recognizing that these are possibilities only and that any one may not necessarily be operative in any single instance.

The first and simplest variable is the size and nature of the wound incident to the introduction of a foreign body. Certain types of foreign body reaction, of course, are not complicated by wounds of entrance, as for instance the reactions of the lung to inhaled dust. So far as surgery is concerned, however, the size of the wound has a bearing on the degree of reaction. It is clear that the larger the wound the greater the original inflammatory reaction preceding repair and the more profuse the elements of repair. In the old controversy involving the merits of absorbable and nonabsorbable suture material, many experimental studies are vitiated by the failure to control this factor. When sutures of comparable diameter are introduced into animals for comparison of reactions, the favorite absorbable suture material has been one of the forms of surgical catgut and the favorite nonabsorbable material has been silk or cotton. The lack of pliability of surgical gut prevents sharp bending of the strand at the eye of the needle. When a strand of surgical gut threaded through the eye of a needle is placed, the wound of passage through the tissue is much greater than that made by the same size of silk, which bends sharply at the eye of the needle. This illustration is presented not to imply that this difference is the major factor determining the observed differences in foreign body reaction

between the two types of material but rather to indicate by example a possible error in experimental conditions that is frequently ignored.

The second variable is the amount of foreign material introduced, a factor always recognized by observers. What is perhaps not so obvious is the relationship of the measured amount to the surface area of the foreign material. If the reaction of the tissue depends in part on either physical or chemical behavior of the foreign material, which in turn may depend on its surface area, the contour of the experimentally introduced substance is all-important. For instance, as has been noted by many experimenters, the reaction to a solid piece of a single metal may be quantitatively different, usually much less, than the reaction to the same amount of the same metal when introduced as a powder.

Another variable related to the physical characteristics of a foreign body is its wetability. A priori, this might seem to be highly important, particularly when one recalls that the speed with which fibrin is precipitated from shed blood is markedly modified by the wetability of the surface with which the blood is in contact. The absence of marked tissue reaction to certain plastic materials would seem to support the idea of the importance of this factor. However, that wetability or nonwetability is not the sole determining factor is demonstrated by the extensive tissue response to such a nonwetable substance as paraffin.

The fourth variable which must be taken into account is the physical quality and the physical behavior of the foreign material dependent on other characteristics than its size and shape and wetability. Here we are concerned with electric potential, crystal structure, piezoelectric qualities and radioactivity. Ultimately, we may learn that the molecular structure of a substance and the physical implications of its molecular configuration are of immense importance.

The fifth variable is the simple one of chemical characteristics and behavior, involving solubility of the foreign substance in tissue fluids. When the material introduced is soluble or contains soluble impurities, cytotoxic effects, hydrogen ion concentration and the formation of secondary substances with different effects on the tissue than the primary substance must be considered. In addition, the relationship between the chemical structure and the tissue enzymes is of importance. An example is the behavior of free fat liberated after rupture of the fat cell membranes by mechanical force. Hydrolysis by lipase occurs with the disappearance of fat as such, the absorption of glycerol and the deposit of insoluble residues such as fatty acids and perhaps cholesterol about which a foreign body reaction occurs. The factor of enzyme action is also to be considered in connection with collagen and other proteins and with various carbohydrate materials such as starch and oxidized cellulose.

Furthermore, one must always consider differences inherent in the host, differences which may not only exist between different individuals of the same species and between individuals of different species but which may also be present in a single individual at different times. Although well-recognized in all modern studies of wound healing, the factor of nutrition is not so apt to be controlled when a study is focused on the foreign body reaction. Another complex individual variable to be considered is the possibility of antigen-antibody reaction. This has been studied frequently in connection with the use of homografts and as a tentative explanation

for the behavior of tissues about surgical gut.[3] It may be of determinative importance in the use of any material containing a possible antigen. In view of the still incomplete knowledge of the effects on tissues of the adrenocortical steroids, the whole complex field of individual variations in endocrine physiology may be involved.

Much of the experimental work that has been done in the past has been carried out without consideration of still other variable factors. One of these is the purity of the material used. Most of the substances studied have undergone processes of manufacture, including treatment with various chemicals. Can one say that the reaction observed around surgical gut is due to the collagen itself or to the chemicals which have been used in its preparation? This may be unimportant in the practical sense, but it is highly important to the understanding of the fundamentals of the foreign body reaction. A striking example of this factor in experimental studies is furnished by the diametrically opposed tissue reaction to different samples of cellophane. Another is the great differences in the purity of metals.

The unsuspected introduction of other foreign bodies besides those under study may invalidate experimentation. It is probable that since the knowledge of the effect of talc on tissue has been defined a large amount of earlier work can be suspect. It is not unlikely that talc was introduced from laboratory gloves into many wounds when other foreign materials were being experimentally placed. Observations in control wounds in the same animal made at the same time may not be valid, since the amount of talc introduced from the gloves is accidental and variable.

From this probably incomplete outline the complexity of the total problem of experimental study of foreign bodies in tissue becomes abundantly clear.

FUNDAMENTAL OBSERVATIONS

Having posed the problem, I shall now attempt to bring together some of the fundamental knowledge of the mechanisms concerned with the foreign body reaction. There is a large amount of literature, with many controversies and sharp differences in conclusions, most of which cannot yet be resolved. No attempt will be made for the purposes of this discussion to give a comprehensive review of the literature. Certain important illustrative studies will be mentioned, but it is possible that equally important fundamental observations may have been omitted. It is a difficult subject to outline logically. At the risk of some overlapping, an attempt has been made to classify reported studies under five headings, namely, (1) metals and alloys; (2) minerals; (3) crystalline organic materials; (4) noncrystalline organic endogenous materials, and (5) miscellaneous exogenous materials.

The field of the metals has been one of the most vigorously cultivated because of the need for finding suitable material for application to bone. It was early recognized that the electrical behavior of metals in tissue might be concerned with the tissue reaction. The approaches have been, first, by a comparison of the electrical

3. Kraissl, C. J.: Intrinsic Factors Altering the Absorption of Catgut, Surg., Gynec. & Obst. **63**:561, 1936. Kraissl, C. J.; Kesten, B. M., and Cimiotti, J. G.: The Relation of Catgut Sensitivity to Wound Healing, Surg., Gynec. & Obst. **66**:628, 1938. Pickrell, K. L.: Studies on Hypersensitivity to Catgut as a Factor in Wound Disruption, Bull. Johns Hopkins Hosp. **64**:195, 1939.

qualities of various metals with the foreign body reaction they produce, and, second, by a study of tissue cultures exposed to metals. As early as 1908, von Baeyer [4] noted the presence of an electric current about metallic foreign bodies in tissue and studied the corrosion that occurred. Orsós in 1925 [5] postulated a battery action on the strength of an observation of radial nerve stimulation occurring in the neighborhood of a plate and screws applied to a fracture of the humerus when the nerve lay in the wound. Zierold in 1924 [6] discussed the relationship of the electrolytes present in body fluids to the dissociation of metallic ions but did not specifically relate the foreign body reaction to the development of electric current. Venable, Stuck and Beach in 1937 [7] brought sharply to attention the development of electric current between different metals placed in tissue dependent on their electric potentials. They made the statement that pure metals are inert but that alloys, commonly used in surgery, will develop a galvanic current if they contain metals, such as iron, which can be acted on by body fluids. Their introduction of an alloy of cobalt, chromium and tungsten, the now well known vitallium, is a matter of recent surgical history. The fact that later a pure metal, tantalum, was found which was well tolerated by tissues tends to confirm their conclusions.

Campbell and his co-workers [8] attempted to differentiate the possible cytotoxic effects of metal from the electrical phenomena by studying various metals in tissue culture, an approach previously made in France by Ménégaux and Odiette.[9] The latter, interestingly enough, used dissimilar metals in tissue culture and found that the retarding effect on cell reproduction was no greater than that of the metals themselves as observed in previous studies. In discussing this problem, Bates, Reiners and Horn [10] have recently confirmed the presence of electrical phenomena with various metals. They point out that the electric potentials of the metals studied correlate directly with the amount of reaction caused in tissue, but they add with admirable caution that this does not constitute proof that the electrical behavior is the cause of the reaction. Evans,[11] in a stimulating study, has observed that when

4. von Baeyer, cited by Orsós, E.: Über strömerzeugende Knochennähte, Zentralbl. f. Chir. **52**:1014, 1925.

5. Orsós, E.: Über strömerzeugende Knochennähte, Zentralbl. f. Chir. **52**:1014, 1925.

6. Zierold, A. A.: Reaction of Bone to Various Metals, Arch. Surg. **9**:365 (Sept.) 1924.

7. Venable, C. S.; Stuck, W. G., and Beach, A.: Effects on Bone of the Presence of Metals: Based upon Electrolysis: Experimental Study, Ann. Surg. **105**:917, 1937.

8. Campbell, E. H.; Meirowsky, A., and Hyde, G.: Studies on the Use of Metals in Surgery: I. Comparative Determinations of the Cytotoxicity of Certain Metals in Fibroblast Culture, Ann. Surg. **114**:472, 1941. Campbell, E. H.; Meirowsky, A., and Tompkins, V.: Studies in the Use of Metals in Surgery: II. Experiments in the Use of Ticonium in Cranial Repair, Ann. Surg. **116**:763, 1942.

9. Ménégaux, G., and Odiette, D.: Influence des métaux couplés sur la croissance des cultures in vitro de fibroblastes et d'ostéoblastes, Compt. rend. Soc. biol. **119**:485, 1935.

10. Bates, J. I.; Reiners, C. R., and Horn, R. C.: Discussion of the Uses of Metals in Surgery and an Experimental Study of the Use of Zirconium, Surg., Gynec. & Obst. **87**:213, 1948.

11. Evans, S. M.: Tissue Responses to Physical Forces: I. Pathogenesis of Silicosis: Preliminary Report, J. Indust. Hyg. & Toxicol. **30**:353, 1948. Evans, S. M., and Zeit, W.: Tissue Responses to Physical Forces: II. Response of Connective Tissue to Piezoelectrically Active Crystals, J. Lab. & Clin. Med. **34**:592, 1949; Tissue Responses to Physical Forces: III. Ability of Galvanic Current Flow to Stimulate Fibrogenesis, J. Lab. & Clin. Med. **34**:610, 1949.

mixed metallic dusts placed in the peritoneal cavity of rats are subjected to an oscillating electromagnetic field passing through the animal's body, increases in the rapidity of development and in the final degree of the fibrous tissue reaction occur as compared to the reaction to the same materials when not exposed to an electromagnetic field. It should be noted in connection with studies of metallic dusts that the great surface area of the foreign material should exaggerate the effects of electrical phenomena. In any event, this approach to the fundamental study of foreign bodies and the reaction of tissue to them is the sort of investigation that should be conducted in many other areas.

In a discussion of the problem of metals, magnesium merits especial comment. It has been of interest to surgeons because of the fact that it is completely oxidized in tissue and, a priori, might seem desirable for suture material and temporary prostheses. Seelig [12] in 1924, Meek, Prendergast, Harrold, and McCord [13] in 1942, and Schulz and Walter [14] the same year have carried out careful work on the behavior of tissue exposed to this metal. In tissue fluids, magnesium rapidly oxidizes, with the formation of hydrogen gas and of magnesium dioxide. In addition, there is possibly a necrotizing effect on cells with an accompanying high-grade tissue reaction. Schulz and Walter observed no tissue response from the injection of the gas but marked reaction from the repeated injection of a filtrate of plasma treated in vitro with magnesium. They measured the hydrogen ion concentration in the tissues and compared it with the level of hydrogen ion concentration lethal to tissue cultures. From these observations, they concluded that the necrosis is the result of the formation of highly alkaline magnesium dioxide and that the degree of tissue reaction is dependent on the amount of necrosis.

I shall now discuss the problem of minerals. On account of the frequency and seriousness of silicosis, mineral dusts have been subjected to considerable basic investigation. Furthermore, on account of the clinical relationship of silicosis and tuberculosis the problem has interested others besides those in industrial medicine. The earlier theories of the severe reaction about particles of quartz were based on the conception that the sharp point of the crystals must become blunted in order to avoid continuous injury to surrounding cells. However, this teleological conception did not explain the continuing and progressive nature of the reaction. It was pointed out by King [15] and others that crystals of carborundum (silicon carbide) are just as hard and as sharp as those of quartz (silicon dioxide) but create minimal tissue reactions. The second theory of the behavior of silica is that of solubility,[16] the slow dissolving of the substance in tissue fluids with cytotoxic effects arising from the solution. This idea has been supported for many years by many observers but is theoretically open to question.

The latest and most stimulating theory is that of Evans.[11] He postulates that since fibrous tissue has one function only, namely, the absorption of mechanical

12. Seelig, M. G.: A Study of Magnesium Wire as an Absorbable Suture and Ligature, Arch. Surg. **8**:669 (March) 1924.

13. Meek, S. F.; Prendergast, J. J.; Harrold, G. C., and McCord, C. P.: Physiologic Action of Metallic Magnesium, J. Indust. Hyg. & Toxicol. **24**:142, 1942.

14. Schulz, R. Z., and Walter, C. W.: Magnesiogenous Pneumagranuloma, J. Indust. Hyg. & Toxicol. **24**:148, 1942.

15. King, E. J.: Solubility Theory of Silicosis, Occup. Med. **4**:1, 1947.

16. Machle, W.: Pathogenesis of Industrial Pulmonary Disease, Radiology **50**:755, 1948.

stress, one must seek for a mechanical stimulus to explain the response known as fibrosis. He has sought for this mechanical stimulus in the field of piezoelectricity. He reasons that if crystals with piezoelectrical characteristics are present in tissue they will be subjected to the mechanical stress of such factors as muscle action and the pulse, which by minute deformation of the foreign particles could result in the development of small quantities of alternating electric current. Conversely, he reasons that the minute electropotential reversals occurring in living tissue could affect the shape of the crystal and thereby create repeated mechanical stress. In an extensive series of studies, he satisfied himself that the degree of foreign body reaction about dusts with asymmetric crystal structure can be correlated with the piezoelectric capacity of the foreign material introduced. From studies still unpublished which he has been good enough to summarize for me,[17] he now feels that "the original conception of piezoelectricity was far too restrictive" since many amorphous and symmetrically crystalline materials are also capable of inducing in tissue electric fields of considerable potential. In a recent communication he states that he now believes that "the reactivity of foreign materials in tissue correlates more with particle size and electroelastic coefficients than it does with solubility." His observations explain many of the hitherto confusing differences in reactions to different substances with related chemical composition, such as, for instance, the differences between the reactions to quartz, and those to carborundum. Evans has concerned himself only with the fibrous tissue response in his studies and has not considered the foreign body giant cell, the development of which must also be explained. One must recognize this study, yet in its infancy, as most intriguing in its conception, and its further development will be watched with interest.

In regard to the effect of minerals on tissue, an interesting phenomenon was reported incidentally many years ago by Clark[18] in connection with a method of studying circulation visually in the rabbit's ear. He had devised several types of window which could be inserted into the rabbit's ear after removal of the skin. One of these methods placed a sheet of mica against living tissue. The remarkable fact is that he could publish photomicrographs of the exposed tissue, at periods as long as a month after insertion of the window, which showed no trace whatever of an inflammatory reaction except at the edge. In his text, he states that some of these windows were observed over periods of several months. Evans' observations on mica showed variable responses.

The surgical significance of talc, now so well known, need not be detailed here, since practically all our knowledge is empirical. It may well fit into Evans' conception. The entire subject of inorganic crystalline materials offers a field in which much fundamental knowledge is being obtained.

The organic crystalline materials which have been observed to create the foreign body reaction are numerous. They may be classified according to their endogenous or exogenous origin. Among the former are cholesterol and the fatty acids following fat hydrolysis through the action of either pancreatic or tissue lipase. Among the latter are certain drugs such as the sulfonamide compounds and fatty acids introduced

17. Evans, S. M.: Personal communication to the author.

18. Clark, E. R.; Kirby-Smith, H. T.; Rex, R. O., and Williams, R. G.: Recent Modifications in the Method of Studying Living Cells and Tissues in Transparent Chambers Inserted in Rabbit's Ear, Anat. Rec. **47**:187, 1930.

experimentally or developed in tissue after the experimental or therapeutic introduction of animal and vegetable oils. A large amount of fundamental experimental work in this connection has come from the study of tuberculosis. Sabin [19] in 1932 studied the fractionated constituents of the tubercle bacillus and its capsule. She concluded that there are three groups of lipids, including many fatty acids from the tubercle bacillus, which are "remarkable stimulants of the cellular connective tissues." It is perhaps appropriate to mention here the work in 1928 of Pinkerton,[20] who studied the reaction in the lungs to vegetable, animal and mineral oils. He observed no reaction from the introduction of vegetable oils, such as sesame oil, poppy seed oil and olive oil and ascribed their inertness to a postulated lack of hydrolyzing enzymes for vegetable fats in animal tissue. The result of the introduction of animal fat, however, was a pronounced fibrosis with giant cell formation. He believed that the degree of this reaction depended on the amount of free fatty acid formed and the speed of hydrolysis of the fat. With mineral oil, there was quick emulsification and phagocytosis without marked tissue reaction. This last observation is not in conformity with clinical and some experimental [21] observations of paraffin oil and camphorated oil in solid tissue.

A number of endogenous materials of noncrystalline character deserve detailed study. These include such substances as the sebum which may escape into the tissue from a sebaceous cyst and the colloid of the thyroid gland which has been observed to create a foreign body reaction when it escapes from the thyroid follicle. Sebum can probably be classed in the group of lipids of endogenous origin, operating through hydrolysis and the deposit of fatty acid. One must also mention the reaction to sperm when it escapes from the epididymis or the vas deferens.[22]

The field of miscellaneous exogenous materials includes suture materials (with the exception of metals) as well as other substances employed clinically. It must be noted that in this area studies made of tissue reactions, have been largely empirical with little attempt at fundamental correlation. The chemical substances concerned, besides those incidental to manufacture, are, of course, exceedingly diverse. They include animal proteins, such as the collagen of the surgical gut suture, the gelatin and the fibrin of modern hemostatics and the protein of silk. They include the polymerized hydrocarbons such as rubber. They include also the polysaccharides of cotton, of the starch powder now widely used in surgery and of oxidized cellulose. Finally, they include the whole field of the newer plastics, such as polyethylene and lucite. The study of these complex and widely differing substances will not be easy, but it would seem that they offer the opportunity to explore fundamental biological processes from a great diversity of approaches. Certainly any study will be unprofitable so long as it is confused by the presence of

19. Sabin, F. R.: Cellular Reactions to Fractions Isolated from Tubercle Bacilli, Physiol. Rev. **12**:141, 1932.

20. Pinkerton, H.: Reaction to Oils and Fats in the Lung, Arch. Path. **5**:380 (March) 1928.

21. Weidman, F. D., and Jefferies, M. S.: Experimental Production of Paraffin Oil Tumors in Monkeys, Arch. Dermat. & Syph. **7**:209 (Feb.) 1923.

22. Friedman, N. B., and Garske, G. L.: Inflammatory Reaction Involving Sperm: Spermatic Granuloma and Granulomatous Orchitis, J. Urol. **62**:363, 1949. Cronqvist, S.: Spermatic Invasion of the Epididymis, Acta path. et microbiol. scandinav. **26**:786, 1949. Steinberg, J., and Straus, R.: Sperm Invasion of the Epididymis, J. Urol. **57**:498, 1947.

known or unknown chemicals incidental to manufacture. Yaeger's study [23] of the differences between the tolerance of cellophanes produced by various processes of manufacture illustrates the precautions that must be observed in drawing conclusions. Why the plastics in general seem well tolerated by tissue is a fascinating field for investigation.

There is one extraordinarily interesting group of studies with unexpected and even amazing results that is not familiar to most surgeons. For many years Speidel [24] has been observing by cinephotomicrography the effects of injury of various sorts on the tissues of the tadpole's tail, being largely interested in the repair of nerves. In the last three or four years his attention has been directed to the foreign body reaction. Of course, since he is dealing with nonmammalian tissue in a particularly mobile stage of development, his observations are not necessarily applicable to the problem in the usual experimental animal or in man. Yet his observations are so different from our usual conceptions of the foreign body reaction, as presented in the early part of this discussion, that they present an arresting picture. Possibly, if the experimental and practical attack on the problem in man could be so thoroughly divorced from variables as Speidel has been able to divorce his experimental attack in the tadpole, much of our confusion would evaporate. Since these studies cut across the lines of our attempted classification of foreign bodies, I have reserved them for the last.

Speidel has introduced an extensive variety of foreign bodies into the tissues of the tadpole's tail in so minute quantities that the dissecting microscope must be employed. The size of the particles chosen varies from 1 to 50 μ; powders and dusts are in the smaller range and fibers in the larger. He has noted as the earliest reaction the appearance of an inflammatory process, which he ascribes to the wound of placement. If he succeeds in placing the foreign body without either wounding or closely approaching a capillary this reaction is minimal and completely resolves in the course of four to seven days. If a capillary is involved, it may last somewhat longer. Its duration and extent is perhaps somewhat modified by the compactness of the mesenchyme in which it appears; the older the tadpole the more extensive it may be. In the meantime, the foreign body is being separated from the tissue in which it lies by a continuous wall of leucocytes which fuse into giant cells. The extraordinary aspect of these observations is that, with one exception, the reaction is essentially the same no matter what the substance introduced. He has employed many different varieties of material, most of which have already been considered as presenting probably different fundamental problems. There is no essential distinction to be observed in the manner in which the tissues of the tadpole's tail react to such fundamentally diverse substances as aluminum, tantalum, carmine, zinc oxide, cotton, silk, nylon, polyethylene, silica, human hair, cellophane, paraffin, tar and others. No factors of wetability, crystal structure, piezoelectric qualities or battery action seem to modify the reaction. The tissues simply muster leucocytes to keep the foreign body from contact with the fixed tissue cells. The sole exception observed by Speidel is the behavior of magnesium. He has watched the oxidation

23. Yeager, G. H., and Cawley, R. A.: Studies on the Use of Polythene as a Fibrous Tissue Stimulant, Ann. Surg. **128**:509, 1948.

24. Speidel, C. C.: Personal communication to the author.

and ultimate disappearance of this metal and has observed an active inflammatory process coincident with the continuing chemical activity of the implant.

The uniform element of the process in all other instances is the leucocyte reaction. Speidel occasionally sees a capsule of laminated material developing in the later stages, after a period of several weeks, interpreted as collagen, with which fibroblasts are associated. He is as yet unable to generalize on the variations between experiments that may result in this phenomenon. It is oftenest seen when fine dusts, such as that of tantalum, are closely packed, although larger fragments of the same metal may not evoke it. The occurrence of the encapsulation reaction seems also to depend somewhat on the density of the mesenchyme. It apparently is totally unrelated to the specific material under study as evidenced by the example just given.

The occurrence of phagocytosis of implanted particles seems to depend entirely on the size of the particle. From this observation, one can think of the walling-off process of large particles by leucocytes and giant cells as a sort of massive cooperative phagocytosis, with many cells sharing the task that is too large for any one. The hardness of the material may also play a part. For instance, a "soft" paraffin is invaded and broken up by leucocytes and the resulting fragments are separately engulfed. On the contrary, a "hard" paraffin is walled off by leucocytes *in toto* just as is any of the metals tested.

Parenthetically, one of Speidel's observations is fascinating. Most of us are accustomed to observing macrophages and giant cells in fixed tissue preparations. It is hard to realize that before fixation these were living cells. Speidel's moving pictures show that the giant cells applied to the surfaces of his implanted particles are in constant motion as long even as 500 days after implantation, although there is little or no migration. Another incidental observation is that the shape of the foreign body influences the reaction. When the particle has sharp points, even though they be only the ragged ends of a fibril of silk, there is a concentration of leucocytes over the jagged projections as though to protect adjacent tissue cells by rounding them over.

Even if allowance is made for the differences in species, Speidel's observations make one wonder whether the empirically observed variations in the reaction of human and animal tissues to different foreign materials may not arise from variables not related to the character of the foreign body itself. It will be interesting to see what observations will result from the study by this technic of other foreign materials of surgical importance.

COMMENT

This summary of scattered and inconclusive fundamental investigations will not permit of the generalization which some day we may be justified in making. Except for the possible implications of Speidel's studies, one might predict that such generalizations will be individual for each of the general classes of material studied rather than in any complete and comprehensive form. Certainly, any generalizations must include the possible variables that have been listed. Perhaps Evans has come closest to a generalization in one class of materials, but even his conclusions cannot yet be firmly accepted.

The traditional empirical method of testing materials for surgical use in the tissues of animals and man is not profitable from the fundamental point of view.

It remains necessary, however, in this era of heretofore unknown chemical compounds. Until prediction is possible, every new compound with possible surgical usefulness must be tested empirically. It is a wasteful and uncertain method. Perhaps we should know enough from an intimate knowledge of all of its physical and chemical properties to predict the reaction of tissues to any new substance, excepting only the possibility of individual allergic responses.

The future course of investigation must entail a closer relationship between surgery and the three fundamental disciplines of chemistry, physics and biology. Increased knowledge will come from efforts by many groups, each adding some small contribution to the total, aided perhaps by the introduction of some new tool. Today we have a possible new tool which has not been applied to many of these fundamental problems, namely, the availability of the hormones of the adrenal cortex. The profound effect of certain of these remarkable substances on repair, as observed in preliminary studies,[25] may possibly permit us later to isolate various elements of tissue reaction and study them separately. This is a fascinating approach to the fundamental problems under consideration.

During the past 10 mo. we have been engaged in the University of Virginia surgical laboratories in a new approach to the problem of foreign body tolerance. Recognizing the fact that a great deal of the later work has been concerned with electrical phenomena and being aware that relatively little work has been done on the electrical phenomena in wounds without foreign bodies, we have sought to obtain a baseline of the latter against which to measure differences in electrical reactions that may occur with the introduction of foreign bodies. The first phase of this work has recently been completed. It is hoped that this approach may furnish information in regard to the role of changes in potential in determining tissue response.

In conclusion, let me speculate somewhat irresponsibly on the attitude of surgeons over the years to the substances which they have employed in surgery. These substances are chosen primarily, of course, for their obvious physical qualities; but sometimes it seems curious that a choice has been made between substances of equally good physical properties on a basis less than rational. One wonders why cotton, the commonest and cheapest fiber available to surgeons, was so late in being accepted for suture material. Perhaps the surgeon instinctively felt that the more exalted silk was more fit for the nobility of the human body and the dignity of his calling. One can speculate in this uncontrolled fashion about other possible adaptations of readily available substances. My plea is only that the extent of our ignorance be recognized and that the challenge of the foreign body be met by a more illuminating approach than the simple trial and error method of empirical observation. The beginnings of such an approach are seen.

25. Ragan, C.; Howes, E. L.; Plotz, C. M.; Meyer, K., and Blunt, J. W.: Effect of Cortisone on Production of Granulation Tissue in the Rabbit, Proc. Soc. Exper. Biol. & Med. **72**:718, 1949. Plotz, C. M.; Howes, E. L.; Blunt, J. W.; Meyer, K., and Ragan, C.: Action of Cortisone on Mesenchymal Tissues, Arch. Dermat. & Syph. **61**:919, 1950. Ragan, C.; Howes, E. L.; Plotz, C. M.; Meyer, K.; Blunt, J. W., and Lattes, R.: Effect of ACTH and Cortisone on Connective Tissue, Bull. New York Acad. Med. **26**:251, 1950. Blunt, J. W.; Plotz, C. M.; Lattes, R.; Howes, E. L.; Meyer, K., and Ragan, C.: Effect of Cortisone on Experimental Fractures in the Rabbit, Proc. Soc. Exper. Biol. & Med. **73**:678, 1950. Howes, E. L.; Plotz, C. M.; Blunt, J. W., and Ragan, C.: Retardation of Wound Healing by Cortisone, Surgery **27**:177, 1950. Alrich, E. M.; Carter, J. P., and Lehman, E. P.: Effect of ACTH and Cortisone on Wound Healing: Experimental Study, Ann. Surg. **133**:783, 1951.

COMPLICATIONS OF INTRAMEDULLARY FIXATION OF FRACTURES OF THE FEMUR

WALTER G. STUCK, M.D.†
SAN ANTONIO, TEXAS
AND
COLONEL MILTON S. THOMPSON
MEDICAL CORPS, UNITED STATES ARMY

A GROWING popularity for intramedullary treatment of femoral shaft fractures is indicated by the increasing number of medical articles and views on the subject in this country. While complications may occur, most are avoidable, and in spite of them, there is a real justification for this trend because the patient is returned to a physiological state and to normal activity at an earlier date. The majority of these possible complications may be avoided by properly selecting the cases, overcoming errors in technique, and insuring adequate after-care.

This paper is based on an analysis of the difficulties encountered in treating 70 fractures of the shaft of the femur with intramedullary fixation since May, 1948, at Brooke Army Hospital, Fort Sam Houston, San Antonio, Texas.

COMPLICATIONS

The first group of complications may be largely avoided by special consideration in selection and treatment.

Telescoping of Fragments of Comminuted Fractures.—This can be prevented if only fractures with large fragments are selected, and if these fragments are stabilized by loops or sutures of wire of sufficient strength or by screws. Stainless steel wire loops of 0.014 in. (0.035 cm.) diameter have a tendency to break, and wire of 0.020 in. (0.05 cm.) diameter is preferable.

Instability of Fixation.—Instability may occur in fractures near either end of the femur, since the nail cannot hold securely in the wider medullary canal, or in the cancellous bone, at these levels. In this series, use of the nail has been successful, however, for three supracondylar and five subtrochanteric fractures, but with the protection of casts and braces, respectively, to prevent angulation.

Failure to Form Callus.—This may occur when a nailed femur has to be treated while the patient is in bed because of associated injuries or other reasons. The complications of treatment in bed include not only the risk of delayed union but the loss of muscle tone, with possible distraction or even rotation of the fragments.

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† Dr. Stuck died on March 21, 1950.

From the Orthopedic Service, Brooke Army Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

Read before the Section on Orthopedic Surgery at the Ninety-Ninth Annual Session of the American Medical Association, San Francisco, June 29, 1950.

Elimination of heavy traction and conscientious exercises of quadriceps and hamstring muscles, with careful observation for distraction, are the best means of contravening these complications. A wire mattress suture, as used by Böhler,[1] to control rotation osteotomies is a wise precaution in cases for which bed care is anticipated.

Shock.—Shock is a complication in which systemic factors play a part. Although postoperative shock from medullary nailing is appreciable, it is entirely comparable with that from any other type of internal fixation of a femoral shaft fracture, and the same criteria of selection apply.

Infection.—Infection is a serious possibility which makes pressure sores, poor skin, and even remote infections definite contraindications to nailing. If an adequate and early débridement is carried out, a fresh compound fracture may be nailed safely a month after a delayed primary closure has healed by first intention. Old healed compound fractures which have been infected may be nailed, but scar excision (and skin graft if necessary) should be done first. We have used nailing in 18 old compound fractures in which the drainage had ceased two weeks to 18 mo. previously. In one, drainage continued slightly for several months but did not prevent the patient from being ambulatory. In a second patient a four-year-old gunshot wound became infected two months after nailing, and drainage continued until amputation was performed.

Metastasis by Nailing.—This is an unusual complication, which occurred in one case, presented here:

A 35-yr.-old woman was admitted to the Hospital in November, 1948, with a pathological subtrochanteric fracture of the left femur (Fig. 1) occurring two years after a radical breast amputation. For fear of transplanting the lesion to the soft tissues by open reduction, a closed nailing was performed and the patient was discharged home on crutches in two weeks. Two months later, roentgenograms showed a new metastatic lesion in the lower part of the femur, which was probably transplanted by the nail. We have not found this complication described in available literature, but when such a possibility is weighed against the desirability of being relieved of pain and being able to walk for some of the remaining weeks of life, the complication seems worth the risk. In February, 1950, the patient died of generalized carcinomatosis, 14 mo. after the nailing.

The second group of complications can usually be avoided by having adequate equipment and using proper technique.

Splitting of the Cortex.—This may be produced by a nail of too large a diameter, and the split may not show on the roentgenogram unless weight bearing causes it to separate. If the split is recognized at operation, a wire loop can be used to maintain the stability of the fixation.

Impaction of the Nail.—Impaction of the nail in the medullary canal, so that it can neither be driven in nor extracted, is a common early experience for users of the nail. An impacted nail may be sawed off with a hack saw and easily withdrawn and replaced after two weeks.

Separation of the Fragments.—This can be caused by too large a nail becoming caught in the distal fragment and forcing the fracture surfaces apart. Such

1. Böhler, L.: Medullary Nailing of Küntscher, translated by H. Tretter, Baltimore, Williams & Wilkins Company, 1948.

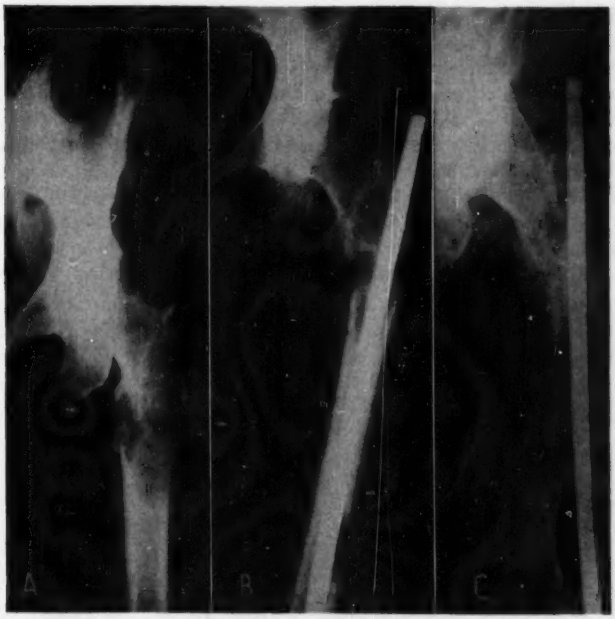

Fig. 1.—Pathological fracture through metastasis from breast cancer. After nailing, a new metastasis is seen distally, possibly transplanted there by the nail. *A*, November, 1948; *B*, January, 1949; *C*, January, 1950.

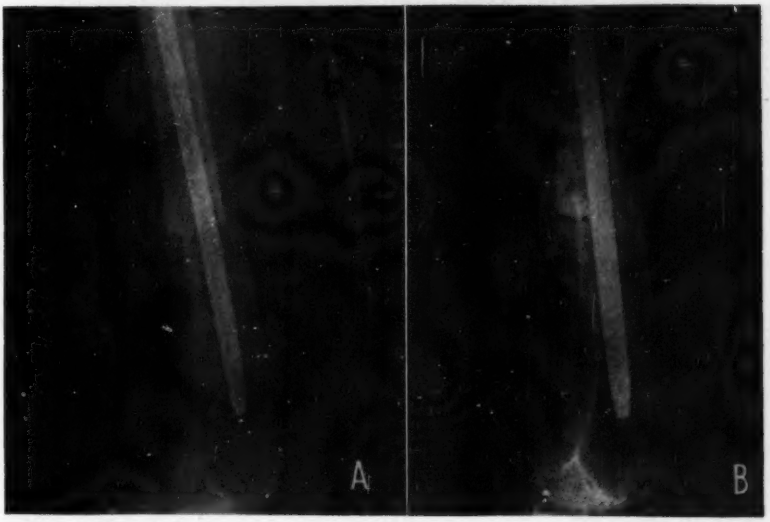

Fig. 2.—Lateral displacement and strong callus. *A*, immediately after operation; *B*, three months later.

separation can be overcome by manual impaction, by exercises to increase hamstring and quadriceps muscle tone, or by partial early weight bearing. These complications, which may accompany the use of nails of larger diameters, may be avoided by using an intramedullary reamer or preferably by using nails of smaller diameter (8 and 9 mm.). It is said that too thin a nail may permit lateral displacement, angulation, or rotation. We prefer lateral displacement (Fig. 2) to absolute apposition because the callus is stronger. The possibilities of angulation (because a thinner nail is more easily bent) and of rotation (because the nail is too small to prevent it) do not nullify the advantages of the small nail. Söeur [2] states that nails less than 9 mm. hold securely because the femur curves in two planes. We are using the smaller sizes, with gratifying results.

Motion at the Fracture Site.—Motion may be expected in fractures of the lower third if the nail is too short. Extended protection or replacement with a longer nail is indicated.

Fig. 3.—*A*, nail penetrating knee joint; *B*, femur 13 mo. later; 100 degrees of knee motion was present.

Pain in the Knee.—Pain may be due to previously unrecognized knee injury. One patient required meniscectomy, and another had ruptured his anterior cruciate ligaments. In one of our early cases, however, knee pain was due to an error in technique in that too long a nail (Fig. 3) had been used and had penetrated the knee joint.

Pain in the Hip Region.—Pain may occur in the hip region if the nail protrudes too far above the trochanter; 2 to 3 cm. of protrusion rarely causes symptoms. Occasionally a nail has been observed to migrate upward, presumably because of motion at the fracture site. Adventitious bursae at the proximal end of the nail have occurred in three cases. The largest was about 500 cc. in size but caused no significant disability even before the nail was removed.

2. Söeur, R.: Intramedullary Pinning of Diaphyseal Fractures, J. Bone & Joint Surg. **28**:309-331 (April) 1946.

Misdirection of Nail.—Misdirection of the nail downward should be no problem under the direct observation of open reduction, but in one case it was found 10 days after nailing that the nail had failed completely to engage the distal fragment (Fig. 4). Misdirection upward, however, is a common error when the proximal fragment is short. In these cases, we expose the trochanter and fracture through a single posterolateral incision and start the nail from above under direct observation at the junction of the trochanter and the superior aspect of the femoral neck. Errors in placement of the nail can be corrected if anteroposterior and lateral roentgenograms are taken before the wound is closed.

Bony Caps.—These may form during the healing period in relation to the head of the nail. We have seen but three, in all of which no guide wire was used, but the

Fig. 4.—Nail in soft tissues, renailed 10 days later. Roentgenograms taken 9 and 10 mo. later showed hip and knee motions normal.

blunt end of the nail was driven upward from below. A causal relationship has not been proved.

Callus Formation.—Delayed callus formation may occur when the time interval between injury and nailing is prolonged. We now arbitrarily use bone grafts in all fractures over one month old.

Fat Embolism.—This is mentioned by almost all authors. Theoretically, medullary callus may create a plunger effect and force fat into the blood stream. It is said, also, that nailing too vigorously may produce fat embolism. Meier [3] reported experiments on dogs in which he found a high fat content in blood from the femoral vein even with the simplest nailing procedure. We have had no

3. Meier, A. W.: Marrow Nail Experiments, read before the Western Orthopedic Association, Santa Barbara, California, Oct. 19-21, 1949.

clinical evidence of fat embolism, but because of the possibility of its occurrence, we prefer to do open reductions in all but the most recent fractures.

Death.—Death in this series occurred once and is described in the following case report:

A 27-yr.-old Negro, weighing 285 lb. (129 kg.), sustained fractures of both femurs when pinned against a garage by a motor car. Two days later open reduction and nailing of both

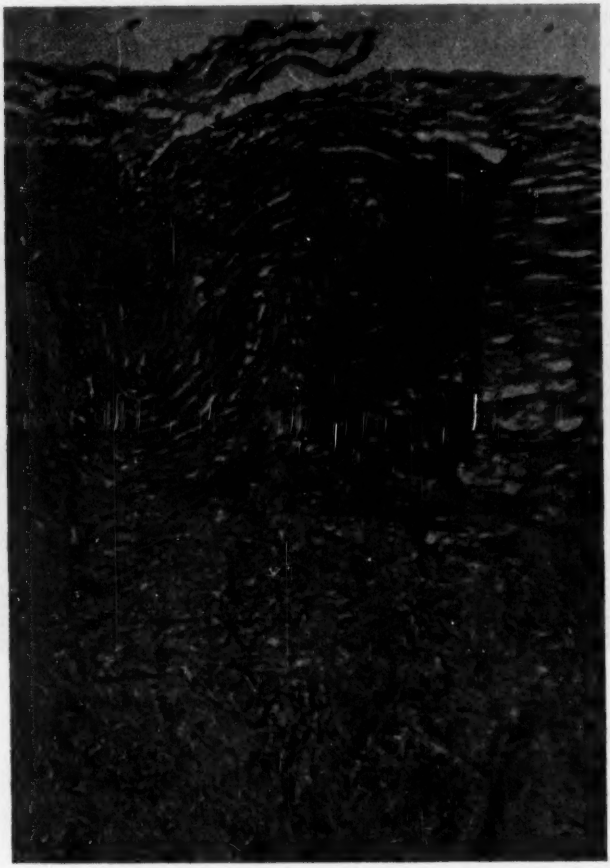

Fig. 5.—Section of membrane surrounding a nail removed nine months after insertion. There is no evidence of chronic inflammatory reaction beyond an occasional lymphocyte and plasma cell.

femurs were performed, after which the patient was in moderate shock. He rallied rapidly, and the postoperative course was uneventful until the eighth postoperative day, when he suddenly became disoriented, the blood pressure dropped, and he died two hours after the onset of symptoms. A diagnosis of lower nephron nephritis was made at autopsy. In retrospect, it is felt that this man should have had his femurs nailed separately, in two operative stages.

The third group of complications occur during the healing period, and their incidence may be diminished by adequate after-care.

Wound Infection.—Wound infection may involve the trochanteric wound, or the thigh wound, or both. Immobilization, drainage, and appropriate antibiotic therapy help to confine the infection to localized osteitis and prevent medullary involvement and osteomyelitis. The nail should not be removed until periosteal bridging occurs. We have had but two instances of infection in femurs but several of infection in other bones treated by intramedullary fixation.

Delayed Union and Nonunion.—These may occur with intramedullary fixation and may be accompanied with bending or breaking of the nail. Early partial weight bearing is important in promoting healing, but if too much weight bearing is permitted too soon, motion at the fracture site may produce nonunion, upward slipping, bending or breaking of the nail. One V type and two cloverleaf type of nails have broken in our series. In all cases there was nonunion, which in our opinion was the cause rather than the result of the broken nail. We have withdrawn and replaced the broken nails and straightened bent nails manually.

Complications in Remote Organs.—Complications such as pulmonary embolism, renal calculi, and thrombophlebitis have not occurred in this series.

Failure to Remove the Nail.—The objections to failure to remove the nail seem to be more theoretical than proved. One objection, raised by Slany,[4] is the reduced capacity of the hematopoietic system as evidenced by the blood picture. He noted an increase in reticulocytes, the presence of young leucocytic forms, and, in some patients, anemia. After removal of the nail, the picture returns to normal. Another objection is that resorption of callus may take place. We feel that this objection has been answered by the recent work of Fitts and others[5] on dogs. They distinguish a periosteal callus, often far removed from the fracture site, which reaches its maximum in four to six weeks and is gradually absorbed. They postulate that the periosteal callus is caused by pressure of the nail on the inner cortex and that its disappearance is due to absorption of bone and release of pressure. The true callus appears at the fracture site about the same time and goes on to consolidation. This point is not finally settled. We do remove the nail after it has been in a year but have no proof that leaving it in situ is detrimental (Fig. 5).

SUMMARY

Intramedullary fixation of femoral shaft fractures returns patients to a physiological state and normal activity sooner than any other method of treatment that we have used.[6]

The majority of the numerous possible complications encountered may be avoided by selecting the proper cases, overcoming errors in technique, and insuring adequate after-care.

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4. Slany, A.: Marknagelung und Blutbild, Arch. orthop. u. Unfall-Chir. **43**:131-147, 1944.

5. Fitts, W. T., Jr.; Roberts, B.; Spoon, S. I., and Ritter, V. W.: The Effect of Intramedullary Nailing on the Healing of Fractures: Experimental Study, Surg., Gynec. & Obst. **89**:609-615 (Nov.) 1949.

6. Stuck, W. G., and Grebe, A. A.: Complications of Treatment of Fractures of the Shaft of the Femur, South. Surgeon **14**:735-754 (Nov.) 1948.

Simple transverse fractures of the middle third of the femur offer the fewest complications. The nearer to either end of the femur the fracture occurs, or the more comminution that exists, the more protection is required proportionately.

Function hastens healing. If early ambulation is not feasible, exercises in bed are essential.

Compound fractures have been nailed, but the risk should be considered.

Transplantation of a metastatic lesion appears possible but is not a contraindication to nailing.

Careful observation of the principles of technique demands intelligent interpretation of preoperative measurements; adequate equipment (including all sizes of nails), instruments, and assistants; roentgenographic control; appreciation of possible errors in the placement and direction of nail, producing distraction, or driving nail too far and of the possibility of a plunger action of the medullary callus or of too vigorous nailing producing fat embolism or contusion of the femoral head, and the realization of the need of bone grafts in certain cases.

Providing adequate after-care means protecting the fracture to the degree, and for the time, that it needs to be protected by cast, suspension, brace or crutches, according to accurate judgment based on observation of the stability obtained at operation, on the weight and reliability of the patient, and on the clinical and roentgenologic appearance of the limb. It means straightening of bent nails with the least possible delay and replacement of broken ones with or without bone graft and the recognition at any time during convalescence of the need of resuming, continuing, or increasing the protection of the fracture.

It is generally agreed that early function lessens the incidence of thrombophlebitis, pulmonary emboli and renal calculi.

Nails are removed after one year, but we have no proof that leaving them in is detrimental.

ABSTRACT OF DISCUSSION

DR. RALPH SOTO-HALL, San Francisco: The technique of intramedullary nailing of femurs is being rapidly improved. There are about fifteen units now studying the problem throughout the United States, and they will convene on September 1. Such a careful and refreshingly honest review of the complications as we have heard today is the type of guidance we need for future progress and should be praised.

We have had our own proportion of instructive and salutary experiences and have come to conclusions which might be helpful in avoiding some of the complications. We have found that an open reduction is preferable to a closed one; it is less hazardous, often more rapid, simplifies the guidance of the pin, and allows the introduction of extramedullary fixation. The adding of some support, to augment the pin's force, is very necessary.

I should like to disagree on one point with Dr. Thompson, and that is in the use of a plaster cast postoperatively. This postoperative fixation defeats the purpose of the nail, which is to give free motion of joints and also, by muscle power, to bring about a contact force which will increase bone union.

With increasing experience, we have learned that the Kuentscher nail often needs something to augment its power of fixation. By adding more internal support, the method is then applicable to a larger group of fractures, particularly those at either end of the shaft. It also increases the stability of comminuted fractures and avoids rotation and distraction, which sometimes may lead to nonunion. The methods of extramedullary splinting, which we have used, have consisted of the following:

[Slide] Here is a pathological fracture. We put a screw through the withdrawal hole of the nail, and since then we have used a longer screw and tilted it more. It gives a good fixation of the upper fragments. Here is a comminuted fracture. For these, we feel that the small segment should be held by a loop of wire, a screw, or a circular band. [Slide] This one, you see, has been held by a small loop, but it adds considerable stability. We have tested it at the operating table.

[Slide] On these long spirals, rather low in the shaft, we feel that some added fixation should also be used. You will notice that the middle one represents a fragment being tested before the nail has penetrated at full length. There is still about 2 in. (5 cm.) above the abducted tuber, whereas in the last we have used a modified Collins band and have introduced the nail to its full depth. [Slide] Here is another spiral fragment. [Slide] Again, using this circular band for increased fixation allows immediate mobility of the joints. I might say that unfortunately I do not have a picture of one complication which we have just encountered, in a woman with a fracture at the same level on her knee, at about the fifth postoperative week. The pin penetrated the knee joint and entered the tibia. [Slide] This is the band which we have been using.

We carried out an experiment by placing a pin of similar size in a vise and applying physical force. We were able, by 100 lb. of pressure, to bend the nail. By bending the nail and then taking the pressure away, we noticed that bending would occur much more easily within 70 or 60 lb. of pressure. In this case we just withdrew the two pins, and that brought the weakened part of the nail above the fracture line.

In 23 nailings, three nails have bent. This problem is a vital one. We have found this complication to occur only with nails under 10 mm. in diameter. For that reason, we advise the reaming out of the narrowed part of the medullary cavity, in the junction of the upper and middle thirds, in order to allow as large a nail as possible to be used. Once a nail has been bent, the metal has been weakened.

We have experimented and proved to our satisfaction that much less force is necessary to rebend a nail which has been previously angulated. One patient, who had both femora nailed, fell, angulating the nail 40 degrees. This was immediately straightened, but by the time the patient had returned to his room, a new angulation had occurred. We found then that we could correct this complication by simply withdrawing the nail about 2 in. (5 cm.), thus moving the damaged part above the fracture line. This avoided an extensive reoperation, and the fracture held well until healing took place.

There is a psychological complication which we have jokingly called "pin euphoria." When a person in whom adequate pinning has been carried out has a feeling of complete solidity and lack of pain in his leg about the third or fourth week, he is given a false sense of confidence which is not warranted by the strain the leg can sustain. We have had patients who at this stage, without permission, have driven automobiles and have committed many other indiscretions which have been difficult to control. A patient was driving a car one month after nailing when he had a head-on collision. This shortened his comminuted fracture about half an inch but did not bend his 10-mm. nail.

I have wondered what the effect of transmitted hammering has been on the hip joint. I should like to ask Dr. Thompson if he believes that the heavy hammering needed at times, for either the introduction or the withdrawal of a pin, could produce vascular changes in the femoral head.

It is our opinion that this method, although crowded with pitfalls and perils, is the most effective form of therapy for properly selected fractures of the shaft of the femur because of its excellent results.

Dr. J. Vernon Luck, Los Angeles: Some of us in Southern California are qualified to discuss the complications and technical difficulties involved in this procedure. We have had every conceivable complication, except the one we most feared and expected, which was catastrophic showers of fat emboli.

We are indeed indebted to the late Walter Stuck and to Colonel Thompson for focusing our attention on this timely subject. It is far more important, at this point in the evolution of the therapeutic method of treatment, to discuss our complications and errors frankly than to revel in our successes.

In general, our complications are similar to those of the authors. In the first comminuted fracture which we treated we did not fix the butterfly fragment. It seemed to set well in position, but within a few days it dislodged and, much to our astonishment, we had nearly 2 in. (5 cm.) of telescoping of the major fragments. Since then, we have fixed this free fragment (one, two, or three fragments) with heavy stainless steel wire and have had uniformly satisfactory results. However, we have not had the courage to allow early weight bearing in cases of comminution. In ununited fractures, we encountered great difficulty in inserting the pin, but since we got an adequate set of reamers we have had no further difficulty on that score.

We have encountered two complications when there was a short distal fragment. In one case, we drove the pin into the knee joint. In our effort to set the pin in as far as possible, we went too far, so at the operating table we withdrew the pin to its proper position. However, it promptly remigrated through the previously prepared channel back into the knee joint. The other complication from a short distal fragment has been angulation without bending of the pin. The pin fills the proximal fragments adequately, but in the distal fragment it does not fill the medullary canal. There has been some angulation and some rotation, but it has not been serious.

With a short proximal fragment, we have had some difficulty in placing the guide pin into its proper position, just anterior to the upper pole of the greater trochanter. We prepared a small tube to insert into the medullary canal with the short proximal guide pin. It had the effect of facilitating the proper insertion and direction of the guide pin.

Pins have migrated proximally in some cases, just as in the authors' experience, and we have seen adventitious bursae develop over these proximal ends and a gluteus medius limp from the bursae and from the mechanical influence of the protruding pin. When the pin was ultimately removed, these difficulties were resolved.

We have had to suffer, like others, through the dramatic experience of lodging a pin in the proximal fragment. We do not now use such a large pin, because we think it need not fit so tightly as we thought it should at the beginning. We lodged the pin so tightly in our first case that we could not get it in or out, and ultimately we used plating and applied a cast incorporating the protruding pin. Two weeks later the pin was removed without difficulty.

When we lodge a pin, we insert one of smaller caliber into the proximal fragment and from below. That has been, in effect, the method of dislodging which we have used.

We have had no experience with the technique of inserting pins without the use of an open reduction. We have enough trouble with the fracture site exposed; I hesitate to contemplate the difficulties we would have were we to use the closed technique. It is heartening to note that one by one the many complications which have plagued us in the use of this audacious technique are becoming preventable.

DR. JORG BOHLER, Vienna, Austria: Our experiences are very similar to Dr. Thompson's. In the Vienna Accident Hospital we have treated about 700 fractures of long bones by medullary nailing. Different methods have proved to be more satisfactory in all other bones but the femur. We therefore used it only for the femur.

I have lately reviewed our femur cases up to 1948, numbering 151. We feel that in properly selected cases medullary nailing is at the moment the best-known method of treatment. Possible complications can be avoided with proper indication and technique. Only a relatively small percentage of all fractures of the femur are suited for medullary nailing.

[Slide] From 1941 to 1948, we treated 988 old and fresh fractures of the femur. Of those, only 151, or 15.3%, were treated by medullary nailing; 251, which is 25.4%, could be treated by Smith-Petersen nailing for intracapsular fracture of the neck of the femur. Other fractures included mostly pertrochanteric fractures and supracondylar and condylar fractures of the femur.

The main advantage of medullary nailing is the stable osteosynthesis. That means that union of the fragments after operation should be so firm that weight bearing can be allowed after wound healing without any other external fixation, such as traction, plaster, or braces. If we cannot achieve this, we do not feel that medullary nailing is indicated.

[Slide] On the next slide it is shown that after some experience we always could get stable osteosynthesis. The numbers in parentheses show the cases with unstable osteosynthesis. In the first half year, we did more closed medullary nailings than in any other year. Among 14 cases, osteosynthesis was not stable in 10 and the operation was not indicated or it should have been opened by means of wire sutures. In the next year, five cases out of nine were not stable.

After the first one and a half years, a follow-up study was done, and the exact rules for indication and technique were given to avoid further complications. The result was that since then all cases have been stable and the operation has been indicated. In the other groups, the results were similar.

The reason for unstable osteosynthesis in the first years in all open reductions is that without penicillin we did not dare to put any additional foreign bodies, such as wire sutures, in the wound, which we do now routinely. Since 1945, stable osteosynthesis has been obtained in all cases with open reduction.

[Slide] The next slides show the results in all our cases. We think that closed medullary nailing is the best method for fresh cases, provided a proper reduction apparatus is used and a well-trained operation team is available. The cases are divided into those covering the first one and a half years and those for the following years. Here again the tremendous difference in the results after sufficient experience can be seen.

In the first one and a half years, we had a total of 23 cases, and in the second year, 35 cases. In the first period the results were excellent in eight cases, good in eight, fair in five, and bad in two. On the other hand, in the second year, there were 25 excellent, four good, four fair, and two bad results. The good and fair results were due to elimination of the motion of the knee joints, mainly from other injuries.

I should like to draw your attention to Group 3, composed of recent compound fractures. We had, altogether, 26, and only one of them had a bad result, due to a shortening of 7 cm. in a badly comminuted fracture, with no additional wire sutures. The two deaths occurred on the first day, as a result of shock.

Simultaneous fractures of the leg or other bones are especially suited for medullary nailing. After the femur fracture is fixed with the nail, the other fractures can be attended to much more easily.

Fractures of the nails occurred in only two cases of nonunion and were typical fatigue fractures. After the nail was replaced through a small incision above the trochanter, union occurred rapidly. In nonunions, we now use routinely an additional bone graft to hasten union. On the other hand, we have treated nonunion in seven cases with closed medullary nailing and, with the exception of one case, union occurred in a relatively short time. All patients were allowed to stand weight bearing after eight to 10 days.

We have never operated on infected fractures; if infection arises, the nail should be withdrawn.

Most complications of medullary nailing can be avoided by operating only in suitable cases and not in cases of post-traumatic shock and by choosing a nail of proper length and thickness.

Dr. Dana M. Street, Memphis: Dr. Thompson has covered the complications of medullary nailing in admirable fashion.

[Slide] I should like to reemphasize the pitfall of the undisplaced comminution. Here we see a fracture with an undisplaced fracture line.

[Slide] After nailing, there is displacement.

[Slide] Supplementary fixation was obviously necessary. The conventional method sometimes leaves much to be desired [slide], and we prefer to fix such comminuted fractures as this [slide] with transfix screws. These are placed tangentially, missing the nail.

[Slide] Massive callus is sometimes seen; in this patient, there was considerable soft tissue.

[Slide] The simpler the operative technique, the fewer the complications due to the operation. If the nail itself is passed retrograde, it must follow the medullary canal, and complications in the guide pin are avoided.

[Slide] So far, in about 75 femurs we have had no nails jammed, so they could either be driven further or extracted.

I should like to comment on this diagram. The medullary canal, as we have found it, is not round in cross section but slightly oval, with a greater diameter in the sagittal plane. Therefore, if the nail is too tight in the transverse plane, we place it in the sagittal plane, giving it the effect of two sides on the same nail.

[Slide] For the low fracture, we prefer the two-pin method of Dr. Rush.

DR. THOMPSON: I am grateful to the discussants for their charitable and contributory remarks.

VAGOTOMY IN THE TREATMENT OF BILIARY DYSKINESIA

GEORGE CRILE Jr., M.D.
AND
D. W. MILLER, M.D.
CLEVELAND

POSTCHOLECYSTECTOMY colic, or biliary dyskinesia, is a poorly defined syndrome which tends to occur in nervous and hypersensitive persons and which can be diagnosed only by the exclusion of organic disease. The cause of the dyskinesia has not been established, but it is supposed by some that spasm of the sphincter of Oddi plays a part in the production of the symptoms.[1]

Biliary dyskinesia may cause symptoms indistinguishable from biliary colic due to a calculus. The patient complains of intermittent attacks of colicky pain in the right upper quadrant and epigastrium which may radiate to the scapula and to the right shoulder. Nausea and vomiting frequently are associated with the attacks. Chills, fever and jaundice do not ordinarily occur.

The possibility of somatic pain as well as stone in the stump of the cystic duct, stone in the common duct, and disease of adjoining viscera (such as duodenal ulcer, recurrent pancreatitis, and renal calculi) must be excluded before the diagnosis can be made. It is with that group of cases in which biliary colic persists in the absence of any demonstrable abnormality that we are concerned.

Many forms of treatment have been employed, most of them aimed at relaxing spasm of the sphincter of Oddi. Antispasmodics including nitroglycerin may be used, but pavatrine® hydrochloride or adiphenine hydrochloride (trasentine®) seems

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From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

1. (*a*) Ivy, A. C.: Motor Dysfunction of Biliary Tract: Analytical and Critical Consideration, Am. J. Roentgenol. **57**:1 (Jan.) 1947. (*b*) McGowan, J. S.; Butsch, W. L., and Walters, W.: Pressure in Common Bile Duct of Man; Its Relation to Pain Following Cholecystectomy, J. A. M. A. **105**:2227 (June 27) 1936. (*c*) McGowan, J. M.; Knepper, P. A.; Walters, W., and Snell, A. M.: Relation of Spasm of Second Portion of Duodenum to Biliary Colic, Surg., Gynec. & Obst. **66**:979 (June) 1938. (*d*) Layne, J. A., and Bergh, G. S.: Experimental Study of Pain in Human Biliary Tract Induced by Spasm of Sphincter of Oddi, ibid. **70**:18, 1940. (*e*) Butsch, W. L.; McGowan, J. M., and Walters, W.: Clinical Studies on Influence of Certain Drugs in Relation to Biliary Pain and to Variations in Intrabiliary Pressure, ibid. **63**:451 (Oct.) 1936. (*f*) Ivy, A. C., and Sandblom, P.: Biliary Dyskinesia, Ann. Int. Med. **8**:115 (Aug.) 1934. (*g*) Snell, A. M.; McGowan, J. M., and Butsch, W. L.: Colics Following Cholecystectomy: Probable Mechanism of Their Production, Rhode Island M. J. **19**:113 (Aug.) 1936. (*h*) Walters, W.: Pain Mechanism in Biliary Disease, editorial, Surg., Gynec. & Obst. **63**:251 (Aug.) 1936.

to be the most effective. Morphine contracts the sphincter and should be avoided for that reason as well as to avoid the danger of addiction.[2]

Several surgical procedures have been tried. Colp [3] reported good results with endocholedochal sphincterotomy. Splanchnic nerve section has been tried with variable results. Lagerlöf [4] denervated the choledochus in 15 patients in whom morphine induced an attack of colic. Gray and Sharpe [5] reported relief of postcholecystectomy colic by removal of a long stump of the cystic duct.

Since the parasympathetic nervous system through the right vagus nerve maintains a tonic control of the sphincter of Oddi,[6] there are theoretical reasons for believing that a right vagotomy should relax the spasm which is assumed to be present in biliary dyskinesia. On this basis we have performed nine vagotomies for biliary dyskinesia since 1946. In five cases, treatment has been by bilateral subdiaphragmatic vagotomy. In the other four cases right vagotomy alone was performed. In all cases organic disease of the biliary tract, kidney, and upper region of the abdomen had been excluded by appropriate studies.

REPORT OF CASES

CASE 1.—The patient was a woman 63 years of age who had undergone a cholecystectomy for cholelithiasis a year before her entry to the hospital.[7]

She complained of severe attacks of epigastric pain of six months' duration occurring either night or day and lasting 10 to 15 minutes. These were severe enough to make her cry and occurred almost daily. She had no chills, fever, nausea, vomiting, or jaundice, and bowel function was normal. Examination revealed diffuse upper abdominal tenderness. Laboratory data including the icteric index and the serum amylase level were normal. Roentgenograms of the upper gastrointestinal tract were normal, and no calculi were visible in the region of the common duct.

On Nov. 12, 1946, a bilateral subdiaphragmatic vagotomy was performed and a small remnant of the stump of the cystic duct was excised. The pancreas appeared normal. The common duct was aspirated, opened and explored, but no stones or obstruction was found. The duct was not dilated and contained normal-appearing bile. It was closed over a T tube. Postoperative convalescence was uneventful, and since a cholangiogram on the seventh postoperative day revealed no obstruction of the biliary ducts, the T tube was removed.

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7. Hunt, H. B.; Hicken, N. F., and Best, R. R.: Exploration of Biliary Ducts by Cholangiography During the Following Operation, Am. J. Roentgenol. **38**:542 (Oct.) 1937.

The patient has been seen periodically since the operation and has had no recurrence of symptoms. Three years after operation she stated that she was completely well.

Comment.—This patient underwent a bilateral vagotomy and also excision of the remnants of the cystic duct and drainage of the common duct, which may have contributed to the excellent result. However, in this instance the stump of the cystic duct was not enlarged or inflamed and the common duct was drained only for a week. It is therefore probable that the vagotomy is responsible for the relief obtained.

CASE 2.—A woman 48 years of age was admitted to the hospital on March 16, 1947, giving a history of attacks of typical biliary colic starting 15 years before. A cholecystectomy had been performed, but the common duct was not explored. Thereafter she was well until five years before her entry. At this time recurring attacks of pain developed in the right upper quadrant and epigastrium radiating to the right shoulder and scapula and associated with vomiting. On two or three occasions she also had chills but no jaundice. The pain was not relieved by eating or by taking sodium bicarbonate.

Examination revealed severe epigastric and right upper quadrant tenderness. Laboratory data including the serum amylase level were normal. Roentgenograms of the esophagus, stomach, duodenum, and chest and a plane roentgenogram of the abdomen were negative. Administration of nitroglycerin, 1/150 grain (0.4 mg.), relieved the attacks on several occasions.

On March 18, 1947, an exploratory laparotomy was performed. The stomach, duodenum, pancreas, intestine, and common duct appeared normal. Aspiration of the common duct revealed normal-appearing bile. A cholangiogram using iodopyracet injection (diodrast®) revealed no obstruction of the common duct, and it was not opened. A bilateral subdiaphragmatic vagotomy was performed.

Convalescence was uneventful except that the patient continued to have mild cramping pain in the epigastrium associated with eructations of foul-smelling gas. Roentgenograms of the stomach on October 30 revealed 10% gastric retention in six hours. She was given bethanechol (urecholine®) hydrochloride, which relieved her symptoms.

Two and one-half years after operation the patient had no symptoms except for periodic fulness in the epigastrium, with belching of foul gas, and an occasional cramp-like pain in the upper abdominal area, relieved by urecholine.®

Comment.—In this instance relief from the biliary colic was obtained for 2½ years. However, the bilateral vagotomy produced a mild degree of gastric retention.

CASE 3.—The patient was a 52-year-old man who complained of intermittent pain in the right upper abdominal quadrant. He had undergone a cholecystostomy in 1924 and a cholecystectomy in 1929 for cholelithiasis. Thereafter he continued to have recurrent attacks of pain located in the right upper quadrant radiating around the right costal margin to the back. These attacks occasionally were accompanied with nausea and vomiting and frequently awakened him during the night. They did not seem to be related to the intake of food, but enemas often gave him relief. He never had chills, fever or jaundice. The attacks occurred more frequently until he was well only about one week of every four.

Examination revealed slight tenderness in the epigastrium and evidence of osteoarthritis. A test meal revealed a free acid level of 38 and a total acid value of 48 units. Gastrointestinal roentgenograms showed a deformity of the duodenal bulb without evidence of an ulcer niche, a finding that is not uncommon after cholecystectomy. The colon was spastic.

An ulcer type of management was started, and he was given physical therapy for his arthritis. At first he seemed to obtain some relief, but attacks of right upper quadrant pain continued, and he was seen intermittently for two years, with no significant physical or roentgenographic findings except the deformity of the duodenal bulb. Eventually the attacks of pain occurred nearly every day and frequently at night.

An exploratory laparotomy was performed, and the first portion of the duodenum was found to be densely adherent to the under surface of the liver. Thorough examination of the duodenum

and stomach revealed no evidence of an ulcer, and it was thought that the deformity visualized on roentgenograms was due to the angulation of the duodenum caused by adhesions. The common duct was smaller than usual after cholecystectomy, the bile was clear, and there was no evidence of stricture. A cholangiogram was not obtained, but the common duct was normal on palpation and inspection. A bilateral subdiaphragmatic vagotomy was performed.

Three and one-half years after operation he stated that he had not vomited since the operation and had had no recurrence of his preoperative pain. Occasionally there was some discomfort in the right side of the abdomen and back, but from his description this discomfort probably was due to his hypertrophic osteoarthritis rather than to a recurrence of biliary dyskinesia.

Comment.—In this case thorough examination of the stomach and duodenum at operation failed to reveal either an ulcer crater or scarring. The symptoms were probably due to biliary dyskinesia, and relief was afforded by bilateral vagotomy for three and a half years.

CASE 4.—The patient was a woman 61 years old who had undergone a cholecystectomy for gallstones five years before. Soon after she returned home a recurrence of her symptoms developed. The pain was even severer than prior to the operation, radiated to her right side and back, and lasted two to three days. A half grain (30 mg.) of morphine was required for relief. Each attack was accompanied with nausea, vomiting, and a temperature ranging from 99 to 100 F. After subsidence of the pain her side remained sore for several days. She was never jaundiced.

Examination showed tenderness in both upper quadrants of the abdomen. Roentgenograms of the chest and the upper gastrointestinal tract, including a plane roentgenogram of the gallbladder, showed no abnormalities.

The attacks of pain continued, lasted longer and were severer. The pain was so excruciating that during the attack the patient said she did not want to live and as many as three hypodermic injections were required. Serum amylase and lipase levels were normal. The sulfobromophthalein test revealed 8% retention in 30 minutes, and an Ewald test meal revealed a free acidity of 26 and a total acidity of 42 units. A roentgenogram of the colon was negative.

Conservative treatment with antispasmodics failed to relieve the pain, and finally it was decided to explore the common duct. The duct was found to be enormously dilated, and there appeared to be a stricture at the distal end. A cholangiogram revealed dilatation of the duct, and the opaque medium passed into the duodenum after considerable hesitation. The duct was explored, and probes were passed into the duodenum. A T tube was placed in the common bile duct. Bilateral vagotomy was performed.

On the sixth postoperative day the patient had an attack of pain similar to her previous episodes, and thereafter she continued to have an occasional attack of colic while the T tube remained in place. Cholangiograms revealed a greatly dilated common duct without calculi, and there was persistent hesitation in the passage of the opaque medium into the duodenum. Three months after operation a cholangiogram revealed fair emptying of the common duct, with only a small amount of methiodal (skiodan®) sodium remaining in the duct at the end of 20 minutes. The T tube was removed.

After this the patient was free of her preoperative colicky pain but complained of occasional distention of the stomach. At times her stomach became sour and she vomited. In reply to a follow-up letter two years after operation, she stated that a recurrence of upper abdominal pain similar to that which she had before operation had developed recently. She was not vomiting and was performing her usual work but with difficulty.

Comment.—Undoubtedly this patient's postoperative symptoms of epigastric distention and distress were due to low-grade gastric retention secondary to bilateral vagotomy. In this instance bilateral vagotomy and drainage of the common duct relieved the biliary dyskinesia for approximately 27 months before symptoms recurred, but the dilatation of the common duct and the narrowing of its distal end raise the question of organic obstruction such as that caused by pancreatitis.

CASE 5.—The patient was a man 43 years old who for six years had had recurring attacks of upper abdominal pain associated with nausea and vomiting. The pain extended over the entire upper abdominal area, was severest in the right upper quadrant, and never radiated to the back or the shoulder. He had no chills, fever, or jaundice. Four years before his gallbladder had been removed, but it had contained no stones.

Examination revealed no abdominal tenderness or masses. Roentgenograms showed a deformed duodenal bulb without evidence of either obstruction or ulcer. Gastric analysis revealed a free acidity of 62 and a total acidity of 80 units.

A typical attack was observed, occurring after breakfast. The patient appeared in great agony, with cramps in the upper region of the abdomen centered in the right upper quadrant. The abdomen was soft, with some tenderness in the right upper quadrant. He was given ergotamine tartrate (gynergen®) and dibutoline sulfate, without relief. Administration of tetraethylammonium chloride made him feel a little better for 20 minutes, but the pain then recurred with increased intensity.

On Sept. 2, 1947, an exploratory laparotomy was performed, which revealed no abnormality of the stomach, duodenum, pancreas or bowel. The common bile duct was not dilated, but the remnant of the cystic duct was found to be 3 cm. long. A cholangiogram on the operating table revealed no stones, and the opaque medium emptied into the duodenum. The redundant portion of the cystic duct was excised, and a bilateral subdiaphragmatic vagotomy was performed. Convalescence was uneventful.

The patient continued to have attacks of pain and vomiting. On Oct. 30, 1947, he returned with a typical attack, and splanchnic blocks gave slight if any relief. It seemed that his retching varied with the amount of attention he received, and the question arose as to whether or not the attacks might be on a psychogenic basis. A neuropsychiatric consultant noted that he seemed well adjusted during the initial interview. Subsequently an interview in which amobarbital (amytal®) was given was nonproductive.

During the first part of 1948 he improved, gained about 25 lb. (11.3 kg.), and for a time felt entirely well. He attributed the relief to his taking dilute hydrochloric acid. However, in a follow-up letter two years after operation he wrote that attacks of pain, nausea, and vomiting had recurred and were as severe as ever.

Comment.—Bilateral vagotomy in this instance was a complete failure, and the period of remission in 1948 cannot logically be ascribed to the operation.

CASE 6.—The patient was a woman 45 years old who had undergone a cholecystectomy 10 years before for right upper quadrant cramping pain and indigestion. She was told that the gallbladder did not contain stones. Thereafter she was reasonably well for seven years, when severe pain typical of biliary colic developed. A year later a stone was removed from the common duct, and her symptoms were relieved.

She remained well for two years, when colicky pain recurred. This pain was localized in the epigastrium and the right upper quadrant and radiated to the back. It occurred both at night and during the day and required morphine for relief. Nausea and vomiting accompanied the attacks, and although jaundice never appeared, the stools became gray. Fried food and fats produced indigestion. At first the colic occurred every six to eight weeks, but gradually the attacks became more frequent until they occurred daily.

When first seen at the Cleveland Clinic, the patient stated that she had had to take morphine, ¼ grain (15 mg.), four times daily for several months, to control the pain and had lost 18 lb. (8.2 kg.) in six months. In addition to the cholecystectomy and choledochostomy, she had undergone appendectomy in 1923 for a ruptured appendix, a partial oophorectomy in 1944 for an ovarian cyst, and a bilateral salpingoophorectomy and hysterectomy in 1948.

Examination revealed tenderness in the right epigastrium on deep palpation and a liver that was palpable on inspiration. The serum bilirubin level was 0.5 mg. and there was a 10% retention of sulfobromophthalein. A roentgenogram of the chest and flat plate of the abdomen were negative except for minimal hypertrophic osteoarthritis of the spine. A urogram revealed no abnormality of the urinary tract.

Because antispasmodics failed to relieve the symptoms, laparotomy was advised, which revealed a normal-sized common duct containing clear bile. No stones could be palpated, and

a cholangiogram revealed prompt passage of the radiopaque medium into the duodenum, with no evidence of stones. Exploration of the esophageal hiatus, stomach, duodenum, pancreas, and small and large bowel revealed no abnormalities. In view of the negative cholangiogram, the common duct was not opened and a right vagotomy was performed. Convalescence was uneventful, and the patient was free of symptoms at the time of discharge.

One year after operation she stated that she had experienced a recurrence of distress, which began two weeks after she returned home. Sometimes the attacks were as severe as before the operation. However, she was doing her normal amount of work and had taken no opiates since leaving the hospital.

Comment.—In this case right vagotomy failed to relieve the pain.

CASE 7.—The patient was a woman 53 years old who for 16 years had suffered recurring attacks of pain in the right upper quadrant associated with nausea, vomiting, and jaundice. Six years previously cholecystectomy and choledochostomy had been performed, with T tube drainage for approximately eight to nine weeks. The patient was told that considerable gravel was removed. She was well thereafter for about eight months, when the colic recurred. From January to August, 1949, these attacks were so severe that she was hospitalized 10 times.

At the time of examination the patient described a constant "misery" in her epigastrium with severe colic occurring about every three weeks. In a typical attack the pain was localized in the right upper quadrant, was sharp and constant, and radiated around the scapula. It usually lasted about six days and was followed by soreness in her right side. Nausea and vomiting accompanied the pain. At times she became slightly jaundiced and noted that her urine was dark yellow. She experienced neither chills nor fever. In six months she lost 54 lb. (24.5 kg.) of weight.

Examination revealed a blood pressure of 204/112, hypertensive heart disease, a large nodular goiter, dorsal kyphosis, and enlargement of the liver two or three fingerbreadths below the costal margin. The serum bilirubin was 3.8 mg. and cholesterol 161 mg. per 100 cc. with 8% retention of sulfobromophthalein in 30 minutes. Roentgenograms of the upper gastrointestinal tract and the chest were normal. The plane roentgenogram of the abdomen revealed some osteoarthritis of the spine. A urogram demonstrated no pathologic changes but did not visualize the kidneys too well. Cystoscopy and retrograde pyelograms revealed no disease of the urinary tract.

Exploratory operation was advised, and choledochostomy and cholangiography were performed. The common duct was moderately dilated but contained clear bile. Probes passed easily into the duodenum. The cholangiogram similarly revealed dilatation of the common duct, with narrowing at the ampulla and delayed emptying. No stones were visualized. Exploration of the abdomen revealed no other abnormalities. The common duct was closed over a T tube, and a right vagotomy was performed.

Two cholangiograms postoperatively continued to reveal some narrowing of the distal end of the common duct and some delay in emptying. However, in 20 minutes all the dye entered the duodenum.

Convalescence was uneventful, and the T tube was removed a month after operation. A year after operation the patient stated that she had continued to suffer attacks of pain as severe as before.

Comment.—This case is unusual in that the patient thought she was jaundiced. The serum bilirubin was slightly elevated, being 3.8 mg. per 100 cc. Clinical jaundice from sphincter spasm is rare and suggests the presence of stone, stricture, or pancreatitis. Perhaps this case should not be included in the biliary dyskinesia group because exploration demonstrated a thickening of the pancreas and cholangiography showed a delay in the emptying of the diodrast® into the duodenum. Right vagotomy has been of no value.

CASE 8.—The patient was a woman 38 years old who had undergone a cholecystectomy four years before for severe colicky pain in the gallbladder region radiating around to the back and up to the right shoulder. She did not have chills, fever, or jaundice. Nine months after the

operation she again began to suffer from colicky lower abdominal pain, which gradually developed into typical gallbladder colic similar to that which she had had prior to cholecystectomy.

At the time of examination the colic was occurring frequently and consisted of abdominal cramps which localized in the right upper quadrant. The pain radiated around to the back and shoulder, lasted two to four hours, and was severe enough to require morphine. At times she became chilly, and she thought that she may have had a low-grade fever. Usually she vomited during the attacks, but she never became jaundiced. She had lost 50 lb. (22.7 kg.) of weight in one year. Her previous operations included appendectomy and uterine suspension.

Examination revealed tenderness in the right upper quadrant and a small umbilical hernia. Laboratory data were normal. Roentgenograms of the chest, esophagus, stomach, duodenum, and colon were normal. A roentgenogram of the lumbar region of the spine revealed some hypertrophic changes.

Medical treatment with antispasmodics was tried, with some transient improvement. However, the pain became fairly constant in a dull form, with sharp attacks occurring about every three weeks. Infiltration of the scar in the right upper quadrant with procaine gave no relief, nor did blocks of the contralateral stellate ganglion.

An exploratory laparotomy was performed. Examination of the esophageal hiatus, stomach, duodenum, intestines, pancreas, liver, and kidneys showed no abnormalities. The common duct was normal in size and contained clear bile. A cholangiogram revealed no dilatation of the common duct or the hepatic ducts and no stones, and the diodrast® drained promptly into the duodenum. The common duct was not opened. A right vagotomy was performed, and the umbilical hernia was repaired. Convalescence was uneventful, and she experienced no more colic while in the hospital although she did complain of persistent dull pain.

Three months after operation there had been no recurrence of the colicky pain, but a dull ache persisted. Eight months after operation the patient stated that she had had occasional attacks of colicky pain. She stated that the pain had recurred four or five times and was similar to that which she had had prior to the operation.

Comment.—In this case right vagotomy failed to relieve recurrent attacks of biliary colic following cholecystectomy.

CASE 9.—The patient was a woman 56 years old who had had frequent and disabling attacks of biliary colic since cholecystectomy for cholelithiasis performed 10 years before.

Physical examination and investigation of the gastrointestinal and urinary tracts showed no abnormalities. At the time of operation a cholangiogram showed the common duct to be normal. There were no abnormalities of the upper abdominal viscera. The common duct was not opened. There has been complete relief of the biliary colic for 10 months following right vagotomy, but the patient complains of pain in the back and mild lower abdominal distress, probably due to arthritis.

Comment.—In this case right vagotomy has relieved attacks of biliary colic for a period of 10 months, but it is too early to evaluate the end result.

COMMENT

Bilateral vagotomy was performed on five patients with biliary dyskinesia. One is completely well, one has had no more colic but continues to suffer from hypertrophic osteoarthritis which existed prior to operation, one is well except for occasional mild distress due to gastric retention, one was well for 27 months but then a mild recurrence of his former trouble developed, and one obtained no relief. The three with good results have been followed for one and a half to three and a half years since operation.

One of the four patients who were treated with right vagotomy alone has been relieved of her pain for ten months, but the other three are not improved. One patient remains free of pain ten months after operation. Cholangiograms were

performed on all but one of the nine patients operated on. For seven of them cholangiograms were made at the time of operation, and in one other a cholangiogram was taken on the seventh postoperative day through a T tube. The latter was the only one in whom the common duct was opened or drained.

In two of the five patients who were subjected to bilateral vagotomy symptoms of gastric retention developed. Right vagotomy theoretically should be the operation of choice for it interrupts the parasympathetic nerve supply to the sphincter of Oddi, leaving most of the vagus supply to the stomach intact through the left vagus. However, in so far as this small group of patients is concerned, the results of right vagotomy do not appear to be as good as those following bilateral vagotomy. This may indicate that the left vagus nerve contributes a few fibers to the sphincter of Oddi, or it may be sheer coincidence.

In every case of postcholecystectomy colic without chills, fever and jaundice, the possibility of biliary dyskinesia should be kept in mind. If the pain is continuous and well localized, procaine should be injected into the abdominal wall at the site of the pain to rule out a somatic origin in the cholecystectomy scar or in intercostal neuritis. If medical treatment fails, if investigation of the gastrointestinal and urinary tracts reveals no abnormalities, and if the attacks are of sufficient severity to warrant reoperation, a cholangiogram should be made on the operating table. If this shows no abnormalities and thorough exploration of the adjacent viscera gives negative findings, the diagnosis of biliary dyskinesia can be established by exclusion and vagotomy can be tried. It is important to remember that right vagotomy alone gives no side effects but bilateral vagotomy may cause retention.

SUMMARY

Nine patients with postcholecystectomy colic have been treated by subdiaphragmatic vagotomy. Cholangiograms were made on all but one patient, and the diagnosis of biliary dyskinesia was made by exclusion of organic disease. Five of the nine were subjected to bilateral vagotomy, with good results in three, improvement in one, and failure in one. The remaining four were treated by right vagotomy alone, with relief of symptoms in one and slight improvement or failure in three. Patients in whom biliary dyskinesia develops usually are nervous and of a type subject to conversion neuroses. Whenever possible, the symptoms should be controlled by medical or psychiatric therapy. If exploration becomes necessary and no organic cause for the pain is found, right vagotomy may relieve the symptoms without producing side effects. Bilateral vagotomy appears to be slightly more effective than right vagotomy in relieving the patient's symptoms but may cause gastric retention.

FAILURE OF THYMECTOMY IN LYMPHATIC LEUKEMIA

G. O. DEAN, M.D.
A. M. EARLE, M.D.
AND
W. A. REILLY, M.D.
LITTLE ROCK, ARK.

ACUTE lymphatic leukemia is a rapidly fatal disease. Simmons [1] recently reviewed the possible role of the thymus in leukemia and noted the experimental work of McEndy and others [2] which indicated that there is a reduction of the incidence of spontaneous leukemia in a high-leukemia stock of mice after thymectomy. The scholarly review of Simmons and his suggestion that thymectomy be tried in lymphatic leukemia led to the performance of this operation in four cases of the disease.

The patients' ages were 18 mo., 2 yr., 3 yr., and 4 yr. Patients 1 and 3 were girls, and Patients 2 and 4 were boys. In each case the diagnosis of leukemia was made from the clinical picture of pallor, petechiae, bleeding tendency, splenomegaly (in three cases), hepatomegaly, generalized lymphadenopathy, a lymphocyte count of 90 to 100%, with an excess of young types, low platelet count, and positive bone marrow findings. It was surmised that the leukemic condition had been present for 1 mo. before thymectomy in Case 1 and for 2½, 3, and 17 mo., respectively, in Cases 2, 3, and 4. Preoperatively all patients had been treated with multiple transfusions and penicillin, with only slight improvement.

The same technic for thymectomy was employed in each case, namely a midline skin incision from just above the sternal notch down to the level of the fifth costal cartilage, a midline splitting and spreading of the sternum from the sternal notch to the level of the fourth costal cartilage, a careful dissection of the thymus from its attachments, with close attention to the ligation of blood vessels, closure of the sternum with large silk sutures, and reapproximation of the anterior sternal periosteum and the skin margins with small silk sutures.

The removed thymuses weighed 3.8, 6, 16, and 18 gm., respectively, in Cases 1, 2, 3, and 4. It is noted that the smallest thymus came from the youngest patient and that the thymus was larger with each year of increase in age. Pathologic study of the thymus glands revealed no abnormal histologic changes except for some cystic degeneration in Case 2.

From the departments of surgery and pediatrics, University of Arkansas School of Medicine, and the Arkansas Children's Home and Hospital.

1. Simmons, V. P.: Thymic Function and Leukemia, Pediatrics **5**:574, 1950.

2. McEndy, D. P.; Boon, M. C., and Furth, J.: On the Role of Thymus, Spleen, and Gonads in the Development of Leukemia in a High-Leukemia Stock of Mice, Cancer Res. **4**:377, 1944.

All patients recovered from the operation. Severe postoperative bleeding and oozing developed in Case 3 which required bilateral thoracenteses and repeated transfusions. From the third day on, however, the postoperative course was uneventful.

EFFECT OF THYMECTOMY DURING THE EARLY POSTOPERATIVE PERIOD

After each thymectomy the peripheral blood counts revealed an increase in the granulocytes to 40 to 60% and a corresponding fall in lymphocytes. This apparently improved blood picture persisted for 28 days in Case 1, 18 days in Case 2, 4 days in Case 3, and 6 days in Case 4. The increases in blood granulocytes lasting from four to six days can possibly be explained by the alarm reaction of Selye.[3] The alarm reaction, however, probably did not account for the granulocyte increase which lasted for 28 and 18 days in Cases 1 and 2. It is noted that the greatest granulocyte response occurred in the two youngest patients, who also had the smallest thymus glands. These two patients also underwent thymectomy earliest in their leukemic state.

Bone marrow studies in three of the patients revealed no appreciable changes two weeks and one month after operation. In the first case, however, the bone marrow revealed a rise in the granulocyte count of from 0 to 19% at one month.

Preoperatively, a large penetrating ulcer of the right cheek had developed in Case 2, and the patient had a persistent temperature elevation varying from 100 to 103 F. He had been treated with penicillin and multiple blood transfusions, but the ulcer continued to enlarge and the septic type of fever persisted. Three days after the operation his temperature became normal and remained normal during the succeeding month. The ulcer also began to heal and was completely healed by the 10th postoperative day. It remained healed until there was a recrudescence of the leukemic picture.

During the early postoperative period all four cases revealed a decrease in the size of the liver, spleen, and lymph glands, a disappearance of anorexia and fatigability and a weight gain of from 3 to 8 lb. (1.3 to 3.6 kg.).

ADRENOCORTICOTROPIC HORMONE

The appraisal of the blood, bone marrow, and physical status in these patients was complicated by the use of adrenocorticotropic hormone (ACTH), which was administered in 12.5-mg. doses every six hours for two weeks and then in 10-mg. doses every six hours for another two to six days. In Case 1 (acute leukemia) the bone marrow studies still showed a 19% granulocyte count and there was considerable physical improvement when administration of ACTH was started five weeks after thymectomy. In Case 2 (acute leukemia) the blood granulocyte response was beginning to wane, but the apparent physical improvement after surgical intervention was still evident when the use of ACTH was started 18 days after thymectomy. In Case 3 (acute leukemia) the ACTH was given 11 days after thymectomy and seven days after the maximum blood granulocyte response was

3. Selye, H.: General Adaptation Syndrome and Diseases of Adaptation, J. Clin. Endocrinol. **6**:117, 1946.

noted. In Case 4 (subacute leukemia) administration of ACTH was started six weeks after thymectomy and after all observed beneficial effects from the operation had subsided.

With the administration of ACTH, each patient showed a temporary response in the peripheral blood comparable to the response observed after thymectomy.[4]

FINAL RESULTS

In every case the leukemic status as observed in the blood, bone marrow, and physical signs reappeared shortly after combined therapy—thymectomy and administration of ACTH—with eventual termination in death. Patient No. 1 lived three and one-half months after thymectomy and four and one-half months after recognition of the disease. Patient No. 2 died seven months and eight days after thymectomy and roughly nine months after the leukemia was noted. Patient No. 3 lived two months after thymectomy and five months after the recognizable onset of the leukemia. Patient No. 4, who was operated on 17 mo. after he became ill with leukemia, died four and one-half months after thymectomy and 21½ mo. after the onset of his disease.

SUMMARY AND CONCLUSIONS

It is probable that the downward course of all four patients would have continued unabated after their temporary response to thymectomy if ACTH had not been administered. The relatively rapid occurrence of death after thymectomy and after ACTH therapy lends evidence to the fact that thymectomy has little or no beneficial effect on the progress of acute and subacute lymphatic leukemia. The temporary granulocyte response after thymectomy as observed in the blood in the four patients and in the bone marrow in one, as well as the short-lived physical improvement observed in all four patients, would not seem to be sufficient to justify the procedure of thymectomy in acute or subacute lymphatic leukemia.

4. Earle, A. M.; Reilly, W. A., and Dean, G. O.: Thymectomy and ACTH in Lymphatic Leucemia, J. Pediat. **1**:63, 1951.

Case Reports

PERFORATION OF COLON FOLLOWING ACUTE NECROSIS OF PANCREAS

Report of Three Cases

W. D. GATCH, M.D.
AND
RICHARD A. BRICKLEY, M.D.
INDIANAPOLIS

WHAT we learned from the following three cases makes us believe that perforation of the colon may be a somewhat frequent complication of acute pancreatitis,[1] that its presence may not be suspected, and that means of preventing, diagnosing, and treating it deserve consideration. Writers have apparently regarded the condition as a rare occurrence, for we have found only brief mention of it.

REPORT OF CASES

CASE 1.—Mrs. C. G., aged 49 (Methodist Hospital Case #49-33892), had had a sudden, agonizing pain in the epigastrium 24 hours before admission. This had occurred without prodromal symptoms at a time that she was in her usual state of health. It was followed soon by vomiting and signs of peripheral circulatory failure. She was admitted to the hospital on Aug. 24, 1949.

Past History.—The patient had had five laparotomies. Three of these had been for operations on her pelvic organs; one, for cholecystostomy, and one, performed in May, 1949, for drainage of a "peritoneal cyst" (this may have been fluid in the lesser peritoneal cavity). Her general health had never been vigorous, but she had had no serious diseases. She may have had attacks of pancreatitis, but we could not be certain of this.

Results of Physical Examination.—The patient was of slender build. She was deeply cyanotic, though her lungs were well aerated. Her pulse could not be counted, and her blood pressure could not be obtained. The abdominal wall was retracted, motionless, and hard. No borborygmi were heard. The red blood cell count was 4,900,000 and the hemoglobin concentration 104% (16 gm. per 100 cc.). The white blood cell count was 11,000, with 87% polymorphonuclear cells. Serum amylase measured 2,260 units. The urine was normal.

Dr. R. A. Solomon made a diagnosis of acute hemorrhagic necrosis of the pancreas and hemoconcentration. After hydration and blood transfusions, the patient's condition gradually improved, though her recovery was retarded by a right pneumothorax discovered shortly after her admission.

The serum amylase reading on Aug. 29 was 400 units. It was 2,286 units on Sept. 12, after a recurrence, on the preceding day, of the symptoms which she had on admission.

W. D. G. saw the patient on Sept. 16 and made a diagnosis of fluid in the lesser peritoneal sac. On Sept. 19 he drained more than 2 qt. (1.9 liters) of thin, blood-stained fluid from this sac through a high, left rectus, muscle-splitting incision and inserted Penrose tubes.

Feces appeared in the drainage on Sept. 21. The fecal discharge evidently came from the colon because it did not excoriate the skin. It had almost ceased by Oct. 6, when the patient went to her home in a distant state. The patient's son informs us that the fistula closed by Oct. 27; that the abscess was redrained on Nov. 1; that she had a cholecystectomy in May, 1950; that in July, 1950, she had an attack in every way like that which brought her to the Methodist

1. Footnote deleted by authors.

Hospital, from which she recovered without operation; that she is now in excellent health and able to drive her car.

CASE 2.[2]—Mrs. N. K., aged 47 (Methodist Hospital Case #49-1393), in the last two years had had a number of illnesses characterized by epigastric pain, nausea, vomiting, and fever. She entered the hospital in mid-November, 1948, with these symptoms in aggravated form. Dr. Loomis then discovered a tender mass under the left costal border. Roentgenograms showed stones in the gall bladder.

By Dec. 15, she had apparently recovered and went home, but after a month and a half she had a relapse for which she reentered the hospital on Feb. 14, 1949.

W. D. G. saw her in consultation with Dr. Loomis on Feb. 19. They agreed on a diagnosis of stones in the gall bladder, hemorrhagic necrosis of the pancreas, and left subphrenic abscess. No estimation of serum amylase had been made. The diagnosis was based on the history, on dulness in the left upper abdominal quadrant, on the presence of fever and leucocytosis, and on fluoroscopic demonstration of elevation and fixation of the left side of the diaphragm.

On Feb. 22 Dr. Loomis drained a large abscess "high in the left upper quadrant" and removed many stones from the thickened gall bladder. He observed fat necrosis, felt a large mass in the tail of the pancreas, and noted that the foramen of Winslow was open. The postoperative course was prolonged and stormy. Discharge of feces from the wound began on Feb. 28. On April 11 Dr. Loomis redrained the left subphrenic abscess. After this, improvement was slow but continuous. The fecal fistula was still present when the patient left the hospital on Sept. 9. She later had it closed in another hospital and is now in good health.

The abscess in this case formed around the tip of the tail of the pancreas in the greater peritoneal cavity. No excoriation of the skin occurred. The fecal drainage, therefore, came from the colon.

CASE 3.—Mr. D. B. J., aged 59 (Methodist Hospital Case #50-31078), entered the hospital on Aug. 14, 1950, at 3 a. m., four hours after the onset of severe epigastric pain and vomiting. He had never had anything like this before. His general condition was excellent. His color was good. We could discover no abnormality of his heart or lungs. The great size of his abdomen made examination of it unsatisfactory, but we were sure of the presence across the epigastrium of pain on pressure. Roentgenograms taken with the patient in the upright position demonstrated no air beneath the diaphragm.

We recorded the following findings: The pulse rate was 100; the blood pressure was 160/90, and the white blood cell count was 13,800, with 90% polymorphonuclear cells.

A serum amylase determination was not available.

We did an immediate exploratory laparotomy through a transverse epigastric incision. The peritoneal cavity contained a considerable quantity of blood-tinged fluid; the body and tail of the pancreas were enlarged and hard; the stomach, duodenum, and gall bladder were normal.

The patient made a good recovery and left the hospital on Aug. 27. He was readmitted on Sept. 29 because of hiccup, vomiting, and pain in the left upper abdominal quadrant. He had lost much weight. The significant findings were (1) bulging of the abdominal wall at the left costal border and dulness on percussion there and (2) forward displacement of the stomach, shown on roentgenographic examination.

On Oct. 2 we drained 2½ qt. (2.4 liters) of slate-colored fluid from the lesser peritoneal sac through a high, left rectus incision and inserted Penrose tubes. We observed much fat necrosis.

No bacteria were present in smears of the fluid.

The patient's postoperative course was afebrile but poor. It was characterized by anorexia, by great loss of weight, and by mental confusion. The wound closed on Nov. 14. The temperature next day rose to 101 F. We probed the wound and drained 1 pt. (473 cc.) of dark, foul-smelling fluid from it. The patient then went home in care of his wife, a nurse. The wound was kept open. The patient's condition remained stationary until Nov. 21, when he died suddenly of an immense hemorrhage into the colon.[3] Some blood also came from the wound.

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2. Dr. N. S. Loomis provided most of the following report.

3. Moynihan, B. Q. A., in Surgery: Its Principles and Practice, edited by W. W. Keen, Philadelphia, W. B. Saunders Company, 1908, Vol. 3, p. 105. Moynihan here refers to the "death of intestinal hemorrhage" of a patient having a pancreatic abscess.

The following were the pertinent observations at autopsy: A narrow sinus passed from the high, left rectus scar into the lesser peritoneal sac. This contained blood clots and foul-smelling, putty-like material. It was lined by hard scar tissue 1 cm. thick. The transverse colon was densely adherent to the wall of this abscess, and three openings between its lumen and the abscess cavity were present. These were just proximal to the splenic flexure. About 50 gm. of the head was all that could be found of the pancreas. The source of the hemorrhage was a perforation of the splenic artery.

COMMENT

The transverse colon is in contact with the lining of the lesser peritoneal cavity and is close to the pancreas. We think it probable that the transverse colon may be injured when pancreatic necrosis occurs.[4] This injury may be due to thrombosis of its veins (we have seen at autopsy thrombosis of the superior mesenteric vein caused by pancreatic necrosis) or to digestion of its wall by trypsin.

Chemical injury, however, was probably not the sole cause of the perforations we here report (1) because the perforations occurred a considerable time (three weeks and more) after the onset of the pancreatic necrosis, and (2) because the absence of excoriation of the skin around the drainage wounds indicated that prolonged leakage of trypsin did not occur. Perforation of the colon by tryptic digestion at the time of an attack of pancreatitis can hardly occur unless injury to the pancreas and to the structures around it is great enough to cause death very soon.

Writers agree that the exudate associated with acute necrosis of the pancreas is at first nearly always sterile.[5] If it so remains, it forms the contents of a pseudocyst; if it becomes infected, it forms a juxtapancreatic abscess. We know that the exudate in Case 3 was at first sterile. That the exudates in Cases 1 and 2 were also sterile at first seems probable. The exudates in all three cases ultimately became infected. The facts seem to indicate that infection was the chief cause of the perforation of the colon in all three patients and of the perforation of the splenic artery in one of them. Perhaps bacteria may pass from the colon through parts of its wall damaged by trypsin.

Our third patient had blind colonic fistulas of which we did not know prior to his death. The autopsy showed that the diagnosis could have been made easily by roentgenographic examination of the colon. This should be done whenever the presence of a perforation seems at all possible.

Measures which may help to prevent this complication of pancreatic necrosis are obvious. We suggest the following:

1. Keep in mind the possibility that perforation of the colon may occur.

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4. Remington, J. H.; Mayo, C. W., and Dockerty, M. D.: Stenosis of the Colon Secondary to Chronic Pancreatitis, Proc. Staff Meet., Mayo Clin. **22**:260-264, 1947. Robinson, H. C., and Alfonito, F. S.: Acute Pancreatitis: Statistical Review of Recorded Experience, Gastroenterology **4**:388-394, 1945. Constricting inflammatory lesions of the splenic flexure of the colon connecting with the tail of the pancreas and secondary to pancreatitis are described by Remington and his associates in two cases of their own and in one of Forlini. Acute and chronic pancreatitis with fat necrosis was noted in the latter's patient at autopsy.

5. Pinkham, R. D.: Pancreatic Collections (Pseudocysts) Following Pancreatitis and Pancreatic Necrosis: Review and Analysis of 10 Cases, Surg., Gynec. & Obst. **80**:225-235, 1945. "Most writers . . . believe that infection develops in these cysts secondary to tissue necrosis rather than after primary infection of the pancreas."

2. Start the administration of antibiotics in large doses as soon as the diagnosis of acute pancreatic necrosis is made.[6] This will probably prevent infection of damaged or necrotic tissue.

3. Make frequent physical and roentgenographic examinations for the presence of fluid in the lesser peritoneal cavity or beneath the diaphragm in the greater peritoneal cavity, and drain these as soon as they are discovered. Use an abundance of Penrose tubes without gauze, and keep them in place for three to four weeks. Thorough drainage is the most important part of the treatment.

4. Should the patient be first seen after he has had a peripancreatic abscess for some time, and should the presence of a perforation of the colon be shown, the treatment should be free drainage of the abscess and administration of antibiotics. Colostomy proximal to the fistula may be necessary in some cases.

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6. Grollman, A. I.; Baum, G. L.; Moss, H. K., and Goodman, S.: Acute Pancreatitis, with Particular Reference to Its Frequency and Difficulties in Diagnosis, Surgery **29**:163-169, 1951.

HEMOPERITONEUM FROM PERFORATION OF THE GALLBLADDER

WILLIAM T. FITTS Jr., M.D.
WILLIAM E. DeMUTH Jr., M.D.
AND
I. S. RAVDIN, M.D.
PHILADELPHIA

PERFORATION of the gallbladder is a rare complication of gallbladder disease. In 1943 Cowley and Harkins [1] collected 12,915 operations on the gallbladder reported in the literature and found that perforation had occurred in 433, an incidence of perforation of 2.8%. The experience at this clinic, recently reported by Fletcher and Ravdin,[2] is similar, with 44 instances of perforation in 2,807 gallbladder operations, an incidence of 1.6%.

Niemeier [3] has classified gallbladder perforations into the following three groups: Group I, chronic perforations with a fistulous communication between the gallbladder and some other viscus; Group II, subacute perforations with the formation of a pericholecystic abscess, walled off by adhesions from the general peritoneal cavity, and Group III, acute perforations into the free peritoneal cavity. Fletcher and Ravdin [2] applying this classification to several reported series of perforations, found the average incidence of the three groups to be as follows: Group I, 16.2%; Group II, 51%, and Group III, 32.8%. It is fortunate that the commonest type is Group II (pericholecystic abscess) because both of the other types have been associated with an extremely high mortality rate.

Hemorrhage as the outstanding manifestation of gallbladder perforation is a most unusual occurrence in this rare complication of gallbladder disease. Mailer [4] in 1939 collected from the literature five cases of massive hemoperitoneum from gallbladder perforation and added one of his own. We have been able to find only one additional case [5] reported since that time.

Within the past three months two patients have been admitted to the Surgical Service of the Hospital of the University of Pennsylvania with perforation of the gallbladder in which hemorrhage was the outstanding feature. One of these (T. C.) had a free massive intraperitoneal hemorrhage following perforation; the other (R. S.) did not have massive bleeding into the free peritoneal cavity, but the perfora-

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Dr. DeMuth is a Fellow of the American Cancer Society.

From the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, and the Surgical Clinic of the Hospital of the University of Pennsylvania.

1. Cowley, L. L., and Harkins, H. N.: Perforation of the Gallbladder, Surg., Gynec. & Obst. **77**:661, 1943.

2. Fletcher, A. G., and Ravdin, I. S.: Perforation of the Gallbladder, Am. J. Surg. **81**:178, 1951.

3. Niemeier, O. W.: Acute Free Perforation of the Gallbladder, Ann. Surg. **99**:922, 1934.

4. Mailer, R.: Spontaneous Rupture of Gallbladder with Massive Intraperitoneal Hemorrhage, Brit. J. Surg. **29**:91, 1939.

5. Hardy, A. E., and Spelman, P. J.: Gallbladder Perforation: Unusual Case with Laceration of Liver and Hemoperitoneum, Rhode Island M. J. **30**:349, 1947.

tion had resulted in a large subhepatic hematoma which was felt before operation. These two cases seemed worthy of reporting; first, because of the rarity of reports of similar cases in the literature, and, second, because we believe that physicians should be alert to the possibility of hemorrhage from the gallbladder. If patients with this grave complication are to be saved, operation must be performed early. Surgeons confronted by massive hemoperitoneum when operating on patients with acute abdominal symptoms should consider the gallbladder as a possible source of bleeding.

REPORT OF CASES

CASE 1.—*Free, massive bleeding into the peritoneal cavity from perforation of the gallbladder.—History.*—T. C., a 66-yr.-old white retired businessman, entered the Hospital of the University of Pennsylvania on March 7, 1951, because of epigastric pain, nausea, and vomiting of 32-hr. duration. For many years he had complained of mild indigestion relieved by alkalis but had never before had an attack of acute abdominal pain and had not been under the care of a physician until the time of the present illness. The patient felt the pain in the epigastrium, with some radiation beneath both costal margins. Several hours before admission he had noticed pain in the left shoulder.

A systemic review revealed that he had noted unsteadiness of gait for several months.

Physical Examination.—The patient appeared older than his stated age of 66 yr. and was obviously in acute distress because of abdominal pain. His face was pale and moist with perspiration, although there was clinical evidence of moderate dehydration. There was no jaundice. The rectal temperature was 99.4 F., the pulse rate 88, the respiratory rate 24, and the blood pressure 190/90. Examination of the heart and lungs showed no significant abnormalities.

Inspection of the abdomen showed little, if any, distention. On auscultation peristaltic sounds were present but were diminished in frequency; their pitch was normal. Palpation revealed epigastric tenderness, with little guarding and no rebound tenderness. Rectal examination revealed no abnormalities.

There was evidence of peripheral arteriosclerosis, and no pulse was felt below the popliteal space on either side.

Laboratory Data.—On the patient's admission, the hemoglobin level was 11.2 gm. per 100 cc. and the leucocyte count 27,000 per cubic millimeter. The urine was normal. A serum amylase determination revealed 45 Somogyi units per 100 cc. Roentgenograms of the abdomen were normal except for two small loops of slightly dilated small bowel which appeared in the left upper abdominal region. An electrocardiogram showed auricular and ventricular extrasystoles and RS-T segment displacement in the chest leads, thought by one medical consultant to be suggestive of posterior myocardial infraction.

Preoperative Course in Hospital.—Intravenous administration of fluids was started, and the patient was watched closely. During the first few hours after his admission, the abdominal tenderness extended throughout the entire abdomen, rebound tenderness became manifest, and the abdomen became distended. The upper part of the abdomen became more resistant to palpation, but no masses were felt. It was decided that operation was mandatory, and it was performed with the patient under general anesthesia five hours after his admission. The preoperative diagnosis was acute mesenteric thrombosis.

Operation (W. T. F.)—The peritoneal cavity was opened through a long right rectus incision. A large volume of blood welled into the wound, and inspection revealed that the entire peritoneal cavity was filled with blood. An intravenous infusion of whole blood was begun immediately. Since the blood supply to the small and large bowel was apparently undamaged, the operator thought that the most probable origin of bleeding was either a ruptured aortic aneurysm or a ruptured spleen. The fact that the patient had had left shoulder pain strengthened the latter possibility. Accordingly, the left upper quadrant was first palpated. Huge quantities of clotted blood were felt in the left subdiaphragmatic area, presumably coming from a ruptured spleen, and the spleen was therefore delivered into the right rectus wound. In delivery, the splenic capsule was torn, but no gross laceration of the spleen could be found, and the latter was removed without difficulty. The remainder of the upper part of the abdomen was

palpated and the site of bleeding then easily found. The gallbladder had ruptured through the fundus about 3 in. (7.6 cm.) proximal to the distal end. Two stones about 3.0 cm. in diameter were lying free in the peritoneal cavity, and a smaller stone was impacted in the ampulla of the gallbladder. As soon as this stone was removed from the gallbladder, normal-looking bile flowed from the cystic duct. Arterial blood was spurting from the ragged edges of the gallbladder perforation. Most of the wall of the fundus of the gallbladder was gangrenous. There were no adhesions about the gallbladder and no pericholecystic abscess. The distal half of the gallbladder was excised through grossly viable gallbladder wall, well below the area of perforation, and the opening closed about a rubber tube which was exteriorized through a stab wound. The gallbladder bed and the splenic bed were drained with Penrose drains. The right rectus wound was closed in layers with surgical gut. A measured 700 cc. of blood had been removed from the peritoneal cavity by suction, and clotted blood and blood removed with sponges or lost on the drapes was estimated to be at least 1,000 cc., so that a conservative estimate of the total blood lost from the gallbladder perforation would, we believe, be 1,500 cc. During the operation the blood pressure and pulse were stable. The time of operation was 90 min.

Postoperative Course.—Within a few minutes after operation the patient's blood pressure fell suddenly to 80/0, the pulse increased to 160, and the heart sounds became distant. He regained consciousness soon after operation but had frequent periods of irrationality. In spite of large quantities of whole blood, the blood pressure remained low and the pulse high, and death occurred from pulmonary edema 36 hr. after operation. Shortly before death an electrocardiogram showed signs that were interpreted by the cardiac consultant, Dr. Joseph Hafkenschiel, as indicating an anterior myocardial infarction. Permission for postmortem examination was refused.

CASE 2.—R. S., a 71-yr.-old white housewife, entered the Hospital of the University of Pennsylvania on the private surgical service of Dr. I. S. Ravdin on Dec. 5, 1950. For the preceding four months she had complained of short attacks of epigastric pain after eating, associated frequently with vomiting. Forty-eight hours before her admission the epigastric pain had become constant and vomiting persistent. She had not been jaundiced.

A systemic review revealed that she had lost 20 lb. (9 kg.) in the year preceding her admission and that she had been hypertensive for many years.

Physical Examination.—The patient was an emaciated woman who appeared to be her stated age of 71 and who was obviously acutely ill and considerably dehydrated. The blood pressure was 188/80, pulse rate 100, respiratory rate 18 and oral temperature 98 F. No jaundice could be detected on clinical examination.

The heart was enlarged and a systolic murmur was present over the apex and a diastolic murmur over the base. No abnormalities were noted on examination of the lungs.

Examination of the abdomen revealed a large mass in the right upper quadrant. This mass seemed about the size of a grapefruit and was exquisitely tender. The liver was slightly enlarged and did not appear to contain the mass, which was thought to be an acutely inflamed gallbladder. Elsewhere the abdomen was soft. Peristaltic sounds were normal.

Laboratory Data.—There was 9.6 gm. of hemoglobin per 100 cc. of whole blood. The white blood cell count was 28,000 per cubic millimeter. The prothrombin determination showed 67% of normal activity, and the serum bilirubin determination gave a direct one-minute reading of 0.06 mg. and a total reading of 0.21 mg. per 100 cc. of whole blood. The urine was normal except for the presence of an occasional red blood cell. A roentgenogram of the abdomen disclosed two slightly distended loops of small bowel in the left upper quadrant and two rounded, opaque shadows in the right upper quadrant, about 2 cm. in diameter, which were thought to be gallstones.

Preoperative Course in the Hospital.—Saline and glucose solutions were given at a constant slow drip for the 10 hr. preceding operation, which was performed with the patient under intercostal block anesthesia with 1% procaine solution.

Operation (I. S. R.)—A right subcostal incision into the peritoneal cavity revealed a large hematoma surrounding the gallbladder and distending the inferior edge of the liver. The right subhepatic space likewise contained several large clots of blood. After removing the clots, the operator located a 4 cm. laceration in the fundus of the gallbladder opposite its hepatic bed. A

stone forceps was passed into the gallbladder and a single large stone removed from the ampulla. No active bleeding was noted. The free peritoneal cavity, examined through the incision, showed no evidence of massive hemoperitoneum. A soft rubber tube was sewed into the gallbladder with two chromic surgical gut purse-string sutures and then brought out through the lateral angle of the wound. A Penrose drain was placed in the subhepatic space and the wound was closed in layers with chromic surgical sutures.

Postoperative Course.—Recovery was slow and was complicated by moderately severe bilateral bronchopneumonia. The patient's temperature reached 101.4 F. (rectal) the first postoperative day and gradually subsided. She was discharged on her 16th postoperative day, at which time she looked and felt well.

COMMENT

An awareness of the possibility of hemorrhage in acute cholecystitis will aid the physician in diagnosing and treating this unusual complication. Certainly early diagnosis is most desirable so that immediate operation may be carried out. Serious hemorrhage superimposed on a free perforation of the gallbladder, which in itself is associated with a mortality of approximately 40%, requires surgical intervention at the earliest possible time. Five out of eight (63%) of the patients with massive hemoperitoneum reported in the literature (including our Case 1) have succumbed before or shortly after operation. The surgeon should remember that massive hemoperitoneum may be the result of a perforated gallbladder. Had this been realized in the operation in Case 1 (T.C.), the gallbladder would have been palpated before the spleen, the perforation of the gallbladder would have been recognized immediately and the operating time considerably shortened. A fatal outcome might thus have been avoided.

The fact that six of the eight patients with massive hemoperitoneum due to perforation of the gallbladder were over 63 years of age indicates that the physician should be especially suspicious of this complication in the elderly patient with an acute abdominal episode associated with gallstone disease. Although the number of cases reported thus far is small, they do add somewhat to the argument for early operation in acute cholecystitis. In a rapidly aging population the incidence of this complication should increase.

Both of the patients reported herein were hypertensive. Although several of the previous reports do not mention blood pressure determinations, the increased blood pressures in our two patients suggest that the hypertensive patient is more vulnerable to this complication. Gangrenous tissue is usually found to be associated with thrombosed blood vessels; it is paradoxical that hemorrhage should result from transection of such vessels at the time of perforation.

SUMMARY AND CONCLUSIONS

Two cases of hemoperitoneum due to perforation of the gallbladder are reported, one a free perforation, without a palpable mass in the gallbladder area and with over 1,500 cc. of blood in the peritoneal cavity, and the other a perforation with a large subhepatic hematoma which could be palpated preoperatively. Both were associated with gallstones. Neither perforation had produced a pericholecystic abscess.

The physician should be especially suspicious of this complication in the elderly hypertensive patient with gallstone disease in whom acute abdominal pain develops. Had it been realized that massive hemoperitoneum could be caused by perforation of the gallbladder, the technical details of the operation in the first case would have been more expeditiously performed.

PATENT OMPHALOMESENTERIC DUCT

HOWARD B. KIRTLAND Jr., M.D.
SAN DIEGO, CALIF.

THERE have been 134 cases of patent omphalomesenteric duct reported, which figure probably does not reflect its true incidence. Of this number, 30 have been complicated by ileal prolapse, with only four operative recoveries. Many of these reports were made before the advent of present-day surgical technics and antibiotic adjuncts. It is thought that today early clinical recognition of patent omphalomesenteric duct and its complications coupled with prompt surgical intervention plus the aid of antibiotics should result in a considerably lower mortality for this condition. Because of this, the successful treatment of a case of patent omphalomesenteric duct with ileal prolapse is deemed worthy of report.

Anomalies in the umbilical region of clinical significance are rare. Consequently, their importance, embryologic origins, and clinical recognition were long ignored. In 1904 Cullen,[1] who up to that time had thought that hernia constituted the main lesion in this locality, was at a loss to explain the presence of adenocarcinoma in the umbilical region of a patient. His search for an answer to this problem culminated in the publication in 1916 of his book "Embryology, Anatomy and Diseases of the Umbilicus." This book contained summaries of all the recorded cases of umbilical abnormalities up to that time and is the basis for most of our present day knowledge of the umbilicus.

CLASSIFICATION OF UMBILICAL ANOMALIES

Trimingham and McDonald [2] classified anomalies in the region of the umbilicus as follows:

I. Alimentary Anomalies
  A. Completely patent omphalomesenteric duct (umbilical enteric fistula)
  B. Partially patent omphalomesenteric duct
    1. Peripheral portion (umbilical sinus)
    2. Intermediate portion (vitelline cyst)
    3. Enteric portion (Meckel's diverticulum)
  C. Mucosal remnant at umbilicus (umbilical "polyp")
  D. Congenital band (obliterated omphalomesenteric duct)

II. Urachal Anomalies
  A. Completely patent urachus (umbilical urinary fistula)
  B. Partially patent urachus
    1. Peripheral portion (umbilical urachal sinus)
    2. Intermediate portion (urachal cyst)
    3. Vesical portion opening into bladder

III. Vascular Anomalies
  A. Persistent omphalomesenteric vessels
  B. Persistent umbilical vessels
  C. Persistent urachal vessels

IV. Somatic Anomalies
  A. Congenital umbilical hernia
    1. Conventional umbilical hernia
    2. Omphalocele
  B. Exstrophy of the bladder
  C. Endometriosis of umbilicus

From the Surgical Service, San Diego County General Hospital.

1. Cullen, T. S.: Embryology, Anatomy and Diseases of the Umbilicus, Together with Diseases of the Urachus, Philadelphia, W. B. Saunders Company, 1916.

2. Trimingham, H. L., and McDonald, J. R.: Congenital Anomalies in the Region of the Umbilicus, Surg., Gynec. & Obst. **80**:152-163 (Feb.) 1945.

ILEAL DIVERTICULA

Kittle, Jenkins and Dragstedt pointed out that one of the earliest descriptions of an intestinal diverticulum was that of the German anatomist and surgeon, Fabricus Hildamus, in 1598. In 1779 Bose showed that the walls of these diverticula contained all the layers of normal bowel and that they were of congenital origin. Much light was shed on the subject by the series of three papers published from 1808 to 1815 by Johann Frederic Meckel, who outlined the developmental embryology and significance of these diverticula.

The diverticula usually arise from the antimesenteric border of the ileum about 80 cm. above the ileocecal valve, although the location varies considerably. Frequently they have their own mesentery arising from the mesentery of the small bowel.

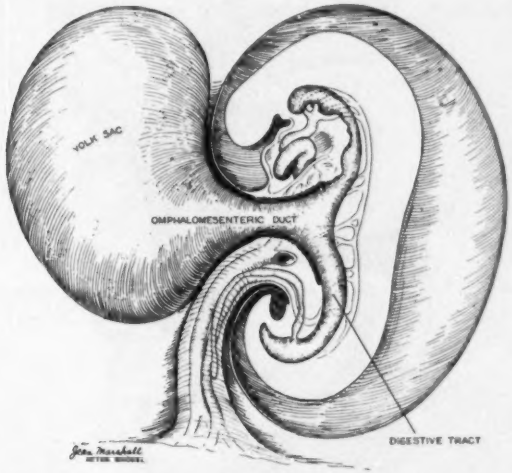

Fig. 1.—3.5 mm. embryo which shows how the omphalomesenteric duct forms the communication between the yolk sac and the developing intestinal tract in the umbilical region.

DEVELOPMENTAL EMBRYOLOGY

Arey [3] stated:

The yolk sac of an early human embryo consists potentially of two regions. Its roof is destined to fold off as a tube which becomes the primitive gut. The remainder is the yolk sac proper, which has no nutritive function but continues to grow into a vesicle about 0.5 cm. in diameter. It may persist throughout pregnancy and appear among the decidua. The isthmus of yolk sac tissue connecting gut with yolk sac proper normally grows at a much slower rate and becomes drawn out into a thread-like duct, the yolk stalk. This stalk is incorporated into the umbilical cord during the sixth week (Fig. 1) but at the same time it usually is also losing connection with the gut. Rapid degeneration and disappearance is the final fate of the yolk stalk.

3. Arey, L. B., cited by Morgan, J. E.: Patent Omphalomesenteric Duct: Review of the Literature and Case Report, Am. J. Surg. **58**:267-274 (Nov.) 1942.

Failure of obliteration of all or part of the yolk stalk results in those anomalies listed under alimentary anomalies. Their relative incidence has been well documented by Thompson.[4]

PATENT OMPHALOMESENTERIC DUCT

This paper is concerned particularly with patent omphalomesenteric duct (Fig. 2). According to Cullen,[1] the first instance of this anomaly was reported by Poussin in 1817 and the first such case with ileal prolapse by King in 1843. Since Cullen's report the literature has been reviewed and brought up to date by Morgan[5] in 1942 and by Kittle, Jenkins and Dragstedt[6] in 1947. In this last article 131 cases of patent omphalomesenteric duct were reported, in 28 of which the ileum had prolapsed through the patent duct. Since then Bronaugh[7] and Arnheim[8] have reported cases of patent omphalomesenteric duct with ileal prolapse, and Fox[9] has reported a case without prolapse. Thus, prolapse of the ileum occurred in 30 of the 134

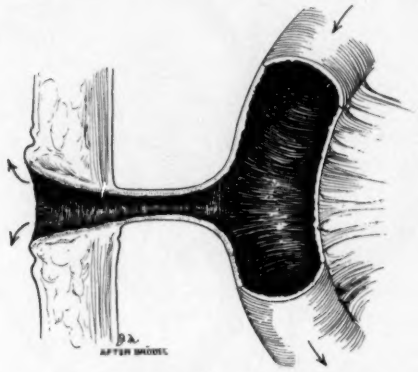

Fig. 2.—Patent omphalomesenteric duct.

reported cases of patent omphalomesenteric duct. There have been four operative recoveries (Cutler[10]; Kittle, Jenkins and Dragstedt; Bronaugh; and Arnheim) in the 30 reported cases with prolapse.

4. Thompson, J. E.: Perforated Peptic Ulcer in Meckel's Diverticulum: Report of Case Occurring Intramesenteric, Ann. Surg. **105**:44-55 (Jan.) 1937.

5. Morgan, J. E.: Patent Omphalomesenteric Duct: Review of the Literature and Case Report, Am. J. Surg. **58**:267-274 (Nov.) 1942.

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Patent omphalomesenteric duct is usually discovered during the first year of life, but cases are recorded in which the condition was not discovered until the patient was in the third decade. It is predominantly an anomaly of the male, occurring in the ratio of eight to one. The umbilical cord is usually thicker than normal at its base. When it separates, it leaves a dimpled red nodule which gradually increases in size until it fills the entire umbilicus and assumes the typical appearance of ileal mucosa. Frequently a polyp may form at the opening. A probe passed into the dimple leads into the ileum. The amount of discharge varies from occasional small

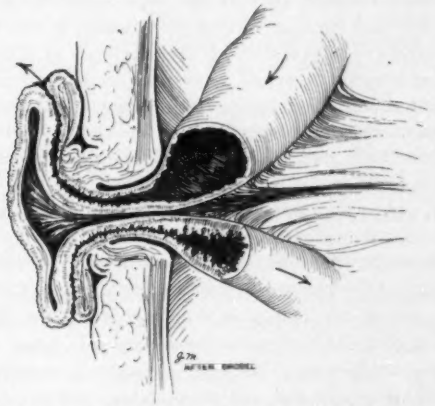

Fig. 3.—Sagittal section of ileal prolapse through a patent omphalomesenteric duct.

Fig. 4.—Frontal view of ileal prolapse through a patent omphalomesenteric duct.

amounts of mucus to a continuous fecal discharge, with considerable irritation of the surrounding skin, depending on the size of the duct and changes in the intra-abdominal pressure. Communication with the gastrointestinal tract may be proved by the ingestion of barium sulfate or a dye such as methylene blue and its subsequent appearance at the umbilicus or by the injection of radiopaque substance into the fistula and the demonstration of the contiguous small bowel by the roentgenograms. Because of the problems associated with the care of a fecal fistula and in order to prevent the occurrence of complications, the patent omphalomesenteric duct should be surgically removed as soon as the child's general condition permits surgical

intervention. Usually excision of the umbilicus followed by removal of the duct at its junction with the ileum is indicated. If the caliber of the duct is large, however, segmental resection of the ileum with the attached duct, with an end-to-end or side-to-side anastomosis, may be necessary.

The most important and serious complication of a patent omphalomesenteric duct is the prolapse of ileum through it on to the abdominal wall (Figs. 3 and 4). Almost all the patients with this complication have been less than 6 months of age, the majority suffering prolapse during the first month of life. This complication has occurred in approximately 20% of the reported cases of patent omphalomesenteric duct. Prolapse requires several predisposing factors such as a duct of good caliber and excessive intra-abdominal pressure such as is produced by crying or by paroxysms of coughing. Actual appearance of the prolapsed ileum may be preceded by a period of obstipation but is often of acute onset. The prolapse presents itself as a dark red, sausage-like mass lying on the abdomen. With prolapse of a single loop, it assumes an S shape. When both afferent and efferent loops prolapse, it is T-shaped. Since the tumor is a portion of bowel that has turned inside out through the patent duct, its surface consists of intestinal mucosa and bleeds readily. At either end there is a dimple representing the openings of the proximal and distal bowel. When seen early, the prolapse may occasionally be reduced manually, in which case resection of the patent omphalomesenteric duct should be done in the usual manner as soon as the change in fluid and electrolyte balance incident to the concomitant intestinal obstruction has been corrected. Later, owing to inability to reduce the prolapse or because of the onset of gangrene, resection of the involved segment along with the patent duct and the umbilicus will be necessary.

REPORT OF A CASE

A 2-mo.-old white boy was readmitted to the San Diego County General Hospital because of a dark red tumor lying on the anterior abdominal wall and arising from the umbilicus. This had appeared during a protracted crying spell between one and a half and six hours previously and had increased in size since its discovery. It was not preceded by anorexia, vomiting or obstipation. In spite of a birth weight of 7 lb. 4 oz. (3.3 kg.), the child had appeared to be premature, as evidenced by deficient nail length, feebleness and lack of normal muscular development. His initial weight loss was excessive, owing to his poor nursing ability. About the third day after birth a small but enlarging red velvety tumor was noted at the umbilicus. After complete slough of the cord the discharge of first mucus, then milk curds, bile, fecal material and ingested methylene blue was noted from a central dimple. A catheter was passed readily through the fistula into the bowel. There were normal stools by rectum. Irritation of the skin of the abdomen by the discharge became a minor problem. A diagnosis of patent omphalomesenteric duct was made. No other congenital anomalies were apparent. It was the consensus of both the surgical and the pediatric service that elective resection of the patent duct should await improvement in the patient's physical condition. His course was followed in the outpatient clinic. He rapidly gained weight and strength. He had been scheduled to enter the hospital for elective resection of the patent omphalomesenteric duct on the day following the occurrence of the prolapse.

On examination, the prolapse was shaped like a T with a short, broad vertical limb, 2 cm. in length, and coiled horizontal limbs, one 7 cm. and the other 15 cm. in length. The bowel was edematous, and the mucosa bled easily and was almost black and gangrenous in appearance. An opening could be identified at either end, but because of the edema neither opening would admit a probe. The prolapse could not be reduced. The child's general condition was good except for moderate anemia.

The stomach was aspirated, and with the patient under open drop ether anesthesia, the abdomen was opened through an incision extending transversely to the right from the umbilicus. Two loops of bowel were found to lead into the mass at the umbilicus. A dense fibrous ring which surrounded the umbilicus was transected, allowing the two loops to be gently withdrawn into the abdomen with the occasional help of an invaginating finger from without. One loop measured 1½ ft. (45.7 cm.) and the other 2 ft. (61 cm.) after reduction, a total of 3½ ft. (106.6 cm.) having been prolapsed. Considerable edema fluid escaped from between the two loops during reduction. When first reduced, the involved bowel was dark, but 10 min. after it was returned to the abdomen, normal color returned except for punctate areas of venous thrombosis in the mesentery. The sheen of the serosa returned, as did normal peristalsis. The prolapse of the patent omphalomesenteric duct was reduced, the umbilical stoma was closed by suture and the umbilicus excised. The mesentery of the duct was divided, and the duct was then amputated at its junction with the ileum and a two-layer aseptic closure of the ileum performed. Both penicillin and streptomycin were instilled into the abdomen, which was then closed. The child withstood the procedure well.

After operation, parenterally administered fluids, glucose, whole blood and penicillin were given and abdominal stupes applied. Streptomycin was administered both intramuscularly and by mouth. The child did well except for transient episodes of abdominal distention. He had normal bowel movements from the first postoperative day, was afebrile after the second postoperative day, and took and retained his formula well the third postoperative day. He was discharged on the 12th day, having gained 1 lb. 10 oz. (0.8 kg.) since entry and has continued to do well.

Pathologic examination of the specimen showed no evidence of aberrant tissue.

This case is a typical illustration of a patent omphalomesenteric duct with ileal prolapse. In retrospect, it is apparent that the extent of the delay of resection of the uncomplicated omphalomesenteric duct incident to the wait for improvement in the child's general condition was ill advised and allowed the occurrence of the ileal prolapse. This is the fifth reported operative recovery from such a condition, which, as previously stated, is probably accounted for by the fact that most of the previously reported cases occurred before the advent of present-day operative technics and antibiotic adjuvants.

SUMMARY AND CONCLUSIONS

Patent omphalomesenteric duct is an infrequently seen umbilical anomaly of clinical significance. Early surgical excision is indicated to end the umbilical enteric fistula and to prevent the serious complication of ileal prolapse through the patent duct. This complication has occurred in over 20% of the reported cases of patent omphalomesenteric duct. In the past it has been accompanied with a high mortality rate, there having been only four reported operative recoveries. Early clinical recognition of the condition and prompt treatment with modern surgical technics and surgical adjuvants should result in a greatly lowered mortality rate.

The case described is the fifth one reported in which there was operative recovery.

AUTOAMPUTATION IN MUCOCELE OF THE APPENDIX

LOUIS SACHS, M.D.
AND
ELMER HOFFMAN, M.D.
BALTIMORE

MUCOCELE of the appendix has been described in the literature under the names of hydrops, retention cysts, cystic disease, cystic dilatation, colloid cysts, mucoid disease and myxoglobulosis of the appendix. Rokitansky [1] in 1842 described mucocele of the appendix. Virchow,[2] in 1863 gave a full pathological description of the disease process. Feré [3] in 1876 named the condition "mucocele of the appendix."

The incidence of mucocele of the appendix at operation is listed in the literature as varying from 0.11 [4] to 0.33%.[5] At postmortem examination the incidence rates vary from 0.04 [5a] to 0.2%.[6] The age range of patients is from 4 to 70 years, with the most frequent incidence being between 42 and 57 years. The ratio of males to females is 1.4 to 1.[5c]

The cause of this disease is obstruction. This view has experimental and clinical support. Grodinsky and Rubnitz,[7] after the work of Wangensteen and Dennis,[8] produced mucocele by washing the lumen of the appendix and then ligating it, while preserving the blood supply. The clinical causes of obstruction of the appendix may be any of the following: (1) focal acute appendicitis, with subsidence and scarring; (2) adhesive bands across the appendix; (3) acute kinking of the appendix due to adhesions or a short mesentery; (4) an appendix which has become closed off from the cecum by the valve of Gerlach,[6a] and (5) tumor of the appen-

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Attending Surgeon (Dr. Sachs) and Resident (Dr. Hoffman), Department of Surgery, Sinai Hospital.

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dix.[9] The secretion of mucus from the tubular mucosal glands may cause dilatation of the appendix distal to the obstruction if the secretion into the lumen exceeds the amount of fluid lost from it by drainage and by absorption. As the intraluminal pressure increases, secretion decreases with atrophy of the glands; and when fluid loss balances fluid secretion, growth of the tumor stops. With this increase in absorption, mineral salts precipitate either as granules in the mucosa or as calculi. The secretion into a mucocele is mucin at first, and then becomes pseudomucin. The contents of a true mucocele are sterile.

Lynch and Dixon[10] postulate a dietary basis for the pathogenesis of mucocele of the appendix. They describe the work of D. P. D. Wilkie, who produced mucoceles in animals fed only a carbohydrate diet.

The size of a mucocele may vary from 3 cm. to that of a football. On gross examination the cyst lining is smooth. It may become unilocular or multilocular. The lumen at the proximal end of the mucocele is closed in most cases but may be patent.[11] Histological examination reveals a picture which varies from an area of no mucosa (due to pressure atrophy) on a thin hyaline membrane to one of normal mucosa, to one of a thickened fibromuscular wall lined by hypertrophied cells.

There is no pathognomonic picture. Most patients give a history of recurrent attacks of pain in the right lower quadrant. There may be a palpable mass. Barium enema may reveal an extrinsic filling defect of the cecum. The temperature and leukocyte count may or may not be elevated. In considering a diagnosis, one must differentiate a mucocele from tumors of the appendix, cecum, intestine, ovary, tubes, uterus or kidney, traumatic hematoma, and intussusception.

The treatment of a simple mucocele consists of appendectomy and removal of the mucocele. The prognosis for an uncomplicated mucocele is excellent. Jones and Carmody[12] list the following complications, resulting from a mucocele of the appendix: (1) intussusception, (2) invagination, (3) volvulus, (4) intestinal obstruction, (5) occurrence in a hernial sac, (6) gangrene and (7) rupture of vessels. Chaffee and LeGrand[13] add carcinoma and pseudomyxoma peritonaei.

We wish to add another complication—autoamputation. The following case is that of a mucocele occupying the entire appendix, self-amputated, leaving the caput cecum free of appendix. A search of the literature failed to reveal any case of autoamputation of a mucocele or of a condition similar to it, with the possible exception of the following statement by Chaffee and LeGrand[13]: "A feature often encountered by surgeons is the occurrence of one or more completely walled-off, mucoid-filled cysts varying greatly in size. These cysts may be close to the appendix or some distance from it." The case which we present here is that of complete autoamputation.

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REPORT OF A CASE

R. C. was a 60 year old white housewife admitted to the hospital on Dec. 29, 1948, with a complaint of upper abdominal pain. Her present illness began suddenly five months before admission with an attack of vague upper abdominal pain, radiating to the right scapular region and associated with nausea and vomiting. She had had one other such attack two months previously. Visualization of the gallbladder revealed the presence of gallstones. The patient entered the hospital for cholecystectomy. Physical examination in the hospital showed a well developed, well nourished white woman about 60 years of age. The temperature was 99 F.; pulse rate, 80; respiratory rate, 18; weight, 135 lb. (61 kg.); height, 62 in. (157 cm.), and blood pressure 170/90 (left arm) and 166/86 (right). Abdominal examination showed slight tenderness on deep palpation in the right lower quadrant. There were varicosities of both greater saphenous systems. There was a small cervical polyp present. Laboratory examinations gave the following results: The urine was normal; the serological test for syphilis elicited a negative reaction; the hematocrit value was 39%; sedimentation rate, 9 mm. per hour; leukocyte count, 9,650, with 40% polymorphonuclear forms, 2% eosinophils, 55% lymphocytes and 2% monocytes; blood urea, 23 mg. per 100 cc.; blood sugar, 60 mg. per 100 cc.; cholesterol esters, 260/179; total protein, 6.2 gm. per 100 cc., with albumin 4.5 gm. and globulin 1.7 gm.; icteric index, 12; direct van den Bergh reaction, 0, and indirect van den Bergh reaction, 0.5 mg. per 100 cc.

At operation, on Dec. 31, 1948, the gallbladder was found packed with stones and the remainder of the biliary tract was normal. The omentum was adherent by a long string of tissue to a mass just over the brim of the pelvis. The mass lay transversely above the bladder, uterus and adnexa. The right half was adherent to the peritoneum overlying the right round ligament and to the mesentery of the terminal portion of the ileum. Its right end lay approximately 4 cm. medial to the caput cecum. The latter was topped by a scar at a point where the three taenia met. There were other adhesions, 5 to 8 cm. in length, from the mass to portions of the jejunum and the terminal part of the ileum. These adhesions carried the blood supply. One of the appendices epiploicae of the sigmoid was adherent to the left end of the mass. No other fragments of the appendix could be found. This mass was removed by severance of its connections with the omentum, ileum, jejunum, sigmoid and right round ligament. Cholecystectomy and cervical polypectomy were then performed. The postoperative course was uneventful.

Pathological Report.[14]—Gross pathological examination of the mass showed it to be sausage-shaped, measuring 13 cm. in length and varying in width from 2.2 cm. at the ends to 4 cm. in the midportion. At one end there was an oval projection measuring 2 by 1.5 by 1.1 cm. The surface was yellowish white. On palpation the mass had a cystic feel. On section the lumen was strikingly dilated and filled with a stringy mucoid material, tenaciously adherent to the wall. The wall averaged 2 mm. in thickness and was distinctly firm. The lining showed the presence of an adherent, whitish, granular, chalky material. Streaks of this extended into the mucoid substance within the lumen. In the end opposite the nodular projection there was a loculation measuring 1.5 by 1 cm. The microscopic sections showed a cystic structure having a hyaline and collagenous connective tissue wall with foci of calcification and mucinous content. These pathological findings are compatible with a diagnosis of an autoamputated mucocele of the appendix.

SUMMARY

A short review of the subject of mucoceles of the appendix has been presented together with a report of a case illustrating a hitherto unreported complication of a mucocele.

14. Courtesy of Dr. Tobias Weinberg, Pathologist-in-Chief and Head, Department of Laboratories, Sinai Hospital, Baltimore.

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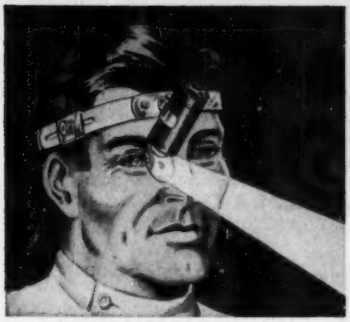

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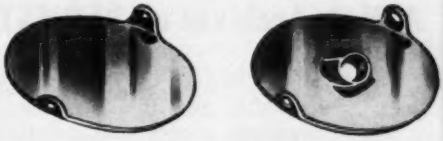

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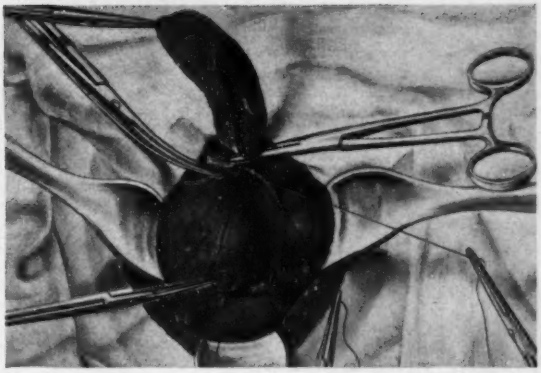

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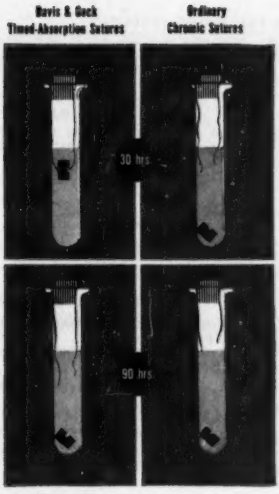

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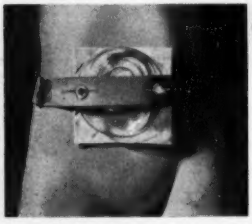

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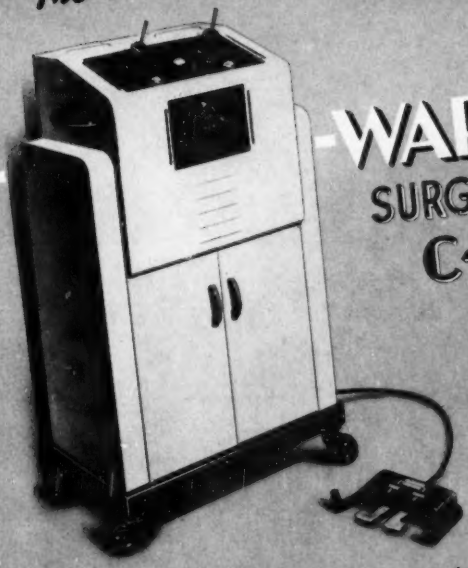

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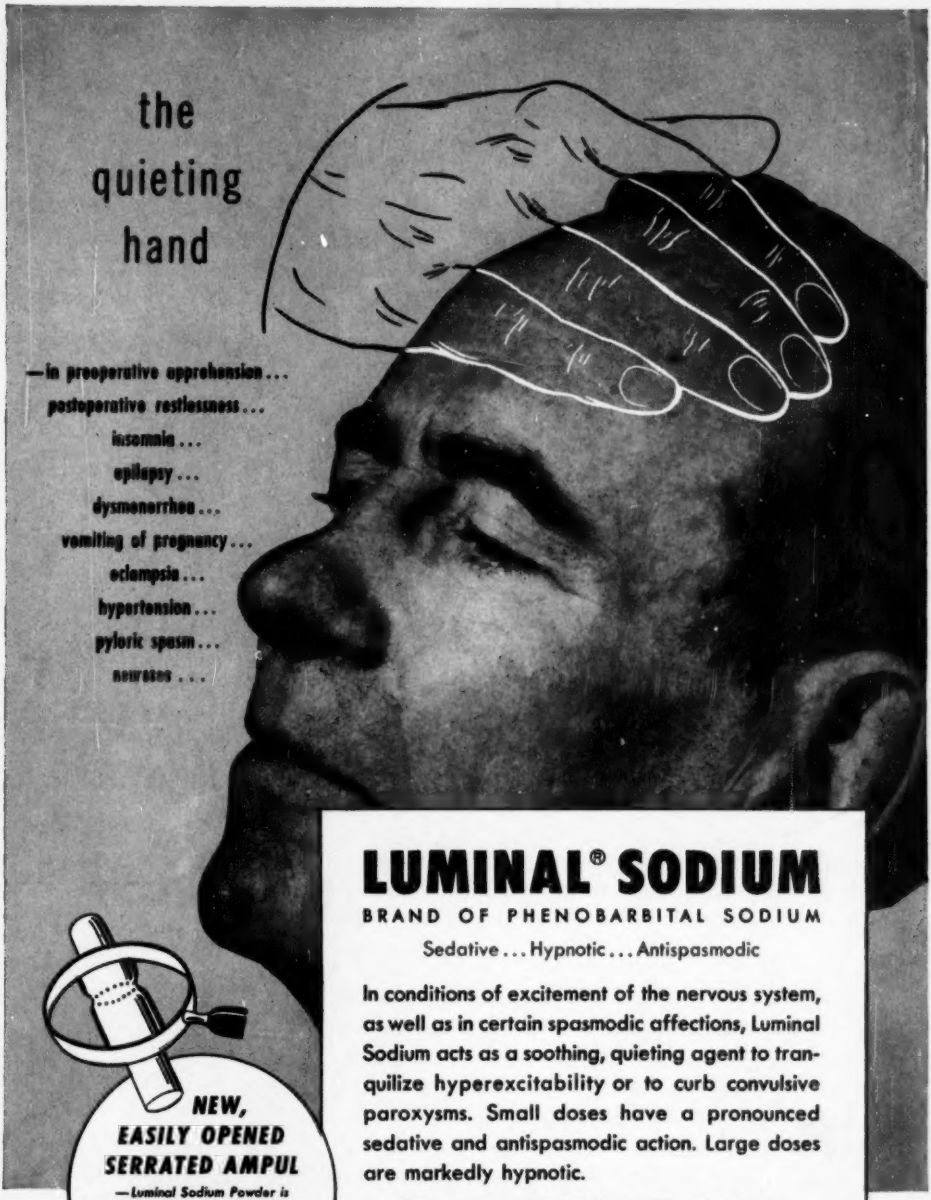

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